

1 UNITED STATES DISTRICT COURT
2 DISTRICT OF NEVADA
3 BEFORE THE HONORABLE MIRANDA DU, DISTRICT JUDGE
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4 AMARIN PHARMA, INC., and :
5 AMARIN PHARMACEUTICALS :
6 IRELAND LIMITED, :
7 : No. 2:16-cv-02525-MMD-NJK
8 Plaintiffs, :
9 : January 14, 2020
10 -vs- :
11 : Reno, Nevada
12 HIKMA PHARMACEUTICALS USA :
13 INC., et al., : Volume 2
14 Defendants. :
15 _____ :

16 TRANSCRIPT OF BENCH TRIAL

17 APPEARANCES:

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(Appearances continue on next page.)

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08:37:38

1 RENO, NEVADA, TUESDAY, JANUARY 14, 2020, 8:30 A.M.

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08:33:18 3
08:33:18 4 THE COURT: Good morning. Please be seated.

08:33:20 5 All right. Counsel, did you resolve the issue
08:33:26 6 with respect to Mr. Klein's demonstrative exhibits yesterday?
08:33:32 7 Is there any objection to the Court attaching them as minutes
08:33:35 8 to yesterday's hearing -- yesterday's trial, I mean?

08:33:37 9 MS. KEANE: Good morning, Your Honor. Meagan
08:33:41 10 Keane.

08:33:42 11 Your Honor, we did have a chance to review the
08:33:46 12 demonstrative. In our view, there is an error that's in the
08:33:50 13 demonstrative with respect to a couple of patents that are
08:33:53 14 actually listed both for the REDUCE-IT indication as well as
08:33:59 15 for MARINE. So we don't think the slide is accurate as it's
08:34:02 16 depicted.

08:34:02 17 What we would propose is that we are willing to
08:34:05 18 work with defendants' counsel to come up with a compromise
08:34:08 19 version that we can agree on and attach that as a
08:34:13 20 demonstrative.

08:34:13 21 THE COURT: You're referring to DX 2699.

08:34:18 22 MS. KEANE: To the summary slide with respect to
08:34:20 23 the list of patents, yes, Your Honor.

08:34:23 24 THE COURT: And that approach sounds agreeable
08:34:26 25 to me. What I was asking, though, is that with the entire set

08:34:30 1 of exhibits that I admitted into evidence but that Mr. Klein
08:34:38 2 had referenced during his cross-examination where he would
08:34:43 3 show the exhibit and then highlight certain portions of the
08:34:47 4 actual exhibit and reference DDX and then the number. That's
08:34:50 5 what I was concerned about.

08:34:52 6 MR. SIPES: We apologize, Your Honor. This is
08:34:53 7 Christopher Sipes.

08:34:54 8 What we thought might make sense, since
08:34:57 9 demonstratives usually wouldn't be attached, would be for
08:35:00 10 defendants to prepare just a chart that correlates the DDX
08:35:04 11 number to the DX number and page. So it would be a simple
08:35:08 12 chart, and that would make the record clear without having the
08:35:11 13 argumentative parts of the demonstrative in, and we could just
08:35:15 14 review that to make sure that it was accurate.

08:35:15 15 THE COURT: I think that would address my
08:35:17 16 concern. All I want is to make sure that there's notation in
08:35:21 17 the record as to whatever the reference is to DDX and then the
08:35:24 18 specific slide number.

08:35:25 19 MR. SIPES: And the advantage of that, that
08:35:26 20 would be a short compact thing that we just would provide the
08:35:29 21 reference, Your Honor.

08:35:29 22 THE COURT: Mr. Klein?

08:35:30 23 MR KLEIN: Your Honor, we can put together that
08:35:32 24 chart if you would like, but there was no argument in any of
08:35:35 25 the demonstratives. You might be thinking of the opening

08:35:38 1 statement. But it was just call-outs.

08:35:40 2 THE COURT: I think the chart serves my purpose.
08:35:43 3 All I want is to make sure that -- there were times when I
08:35:46 4 thought that you didn't note the actual page of the exhibit
08:35:49 5 but you noted the DDX number for certain exhibits that you
08:35:53 6 were showing, that it's clear for the record which page of the
08:35:56 7 actual exhibit you were referring to.

08:35:58 8 So the chart will suffice, and the chart will
08:36:00 9 then be attached to yesterday's trial minutes.

08:36:03 10 MR KLEIN: Okay. Thank you.

08:36:04 11 THE COURT: All right.

08:36:04 12 And then on Exhibit 2299, I'm pretty sure that's
08:36:09 13 the one that's left that I need to resolve; is that right?

08:36:12 14 THE CLERK: Yes.

08:36:15 15 THE COURT: That the parties will confer and let
08:36:17 16 me know if you are able to reach a resolution.

08:36:20 17 MS. KEANE: Okay. Thank you, Your Honor.

08:36:21 18 THE COURT: All right. Let's proceed with
08:36:23 19 Amarin's next witness.

08:36:26 20 MR. M. KENNEDY: Your Honor, this is Michael
08:36:30 21 Kennedy for Amarin. Amarin calls Dr. Matthew Budoff.

08:36:34 22 THE COURT: Thank you.

08:36:37 23 MR. M. KENNEDY: Your Honor, we have some
08:36:39 24 demonstratives with this witness as well as a witness binder.
08:36:42 25 Permission to approach to distribute the binder, and if Your

08:36:45 1 Honor would like a copy of the slides as well.

08:36:48 2 THE COURT: I do not, but I don't want to have
08:36:50 3 the same problem with reference to the page number of the
08:36:53 4 slides. So if the slide is referenced as an exhibit, then you
08:36:55 5 need to reference the actual page number of that exhibit.

08:36:59 6 MR. M. KENNEDY: Understood, Your Honor.

08:37:01 7 THE COURT: Thank you.

08:37:01 8 MATTHEW BUDOFF, M.D.,
08:37:01 9 called as a witness on behalf of the Government,
08:37:01 10 was sworn and testified as follows:

08:37:10 11 THE CLERK: Please be seated.

08:37:14 12 State for the record your full name and spell
08:37:27 13 both your first name and your last name.

08:37:30 14 THE WITNESS: Matthew Budoff; M-a-t-t-h-e-w,
08:37:34 15 B-u-d-o-f-f.

08:37:48 16 MR. M. KENNEDY: Good morning, Dr. Budoff.

08:37:52 17 THE WITNESS: Good morning.

08:37:52 18 DIRECT EXAMINATION

08:37:53 19 BY MR. M. KENNEDY:

08:37:53 20 Q Are you currently employed?

08:37:54 21 A Yes.

08:37:54 22 Q Where are you employed?

08:37:54 23 (Discussion held off the record.)

08:37:54 24 BY MR. M. KENNEDY:

08:37:57 25 Q Dr. Budoff, where are you employed?

08:37:59 26 A I'm employed at the David Geffen School of Medicine at

08:38:04 1 UCLA, formerly known as the UCLA School of Medicine, as well
08:38:09 2 as the Lundquist Institute which is a research institute at my
08:38:13 3 home institution.

08:38:14 4 Q At a very high level, please describe your job
08:38:16 5 responsibilities in those roles.

08:38:19 6 A Yes. So my primary responsibility is teaching. I am the
08:38:23 7 program director for the Division of Cardiology, which means I
08:38:27 8 teach all of the cardiology fellows, those people who are
08:38:30 9 doing three years of advanced training in cardiology, on how
08:38:34 10 to practice cardiology.

08:38:36 11 I also have the opportunity to teach residents,
08:38:38 12 medical students, and other clinicians.

08:38:42 13 And then, when I'm not teaching, I'm either doing
08:38:45 14 clinical work, seeing patients directly, or doing clinical
08:38:49 15 research.

08:38:50 16 Q Were you retained as an expert by a party in this case?

08:38:53 17 A Yes.

08:38:53 18 Q Which party?

08:38:55 19 A Amarin.

08:38:55 20 Q So at a very high level what were you asked to do in this
08:38:59 21 case as an expert?

08:39:00 22 A Yes, I was asked to opine on the patents and understand
08:39:06 23 if there would be infringement in this case if a generic
08:39:10 24 version of a product was brought to market.

08:39:12 25 Q Do you specialize in a particular area of medicine?

08:39:15 1 A Yes.

08:39:16 2 Q What area?

08:39:16 3 A It's called cardiovascular medicine or commonly known as
08:39:22 4 cardiology.

08:39:23 5 Q What is cardiology?

08:39:25 6 A Cardiology is the practice of evaluating the heart.

08:39:28 7 Q Do you have a subspecialty within cardiology?

08:39:32 8 A Yes, I'm a preventive cardiologist.

08:39:34 9 Q What is a preventive cardiologist?

08:39:37 10 A So a preventive cardiologist works to try to prevent
08:39:41 11 either the first heart attack in those patients at high risk
08:39:45 12 of heart disease, or the second heart attack, what we call
08:39:50 13 secondary prevention, in those patients who have already
08:39:52 14 suffered a cardiovascular event.

08:39:54 15 Q Are there other subspecialties within cardiology that
08:39:57 16 you're familiar with?

08:39:57 17 A Yes.

08:39:57 18 Q Such as?

08:39:59 19 A There's imaging, there's invasive cardiology, those
08:40:02 20 people who spend most of their time putting in stints and
08:40:05 21 bypass and other devices, and then there's general cardiology
08:40:10 22 as well.

08:40:10 23 Q How long have you characterized yourself as specialist in
08:40:13 24 preventive cardiology?

08:40:15 25 A About 20 years.

08:40:16 1 Q How long has the field of cardiology recognized
08:40:20 2 preventive cardiology as a subspecialty?

08:40:23 3 A It's been about ten years since it was formalized as a
08:40:26 4 subspecialty.

08:40:27 5 Q So what did you call yourself before preventive
08:40:29 6 cardiology was formalized as a subspecialty?

08:40:32 7 A So if there was no check box that said preventive
08:40:35 8 cardiologist, then I generally -- I would have to refer to
08:40:38 9 myself as a general cardiologist.

08:40:41 10 MR. M. KENNEDY: Mr. Brooks, can we have
08:40:43 11 Plaintiffs' Exhibit 1161, please.

08:40:43 12 BY MR. M. KENNEDY:

08:40:55 13 Q And, Dr. Budoff, you should have this document on your
08:40:58 14 screen as well.

08:40:58 15 A Yes.

08:40:59 16 Q Do you recognize this document?

08:41:00 17 A Yes.

08:41:01 18 Q What is it?

08:41:01 19 A It's my curriculum vitae or CV.

08:41:06 20 Q What does your curriculum vitae contain in general?

08:41:10 21 A It goes through my education, training, my current work
08:41:15 22 and prior work opportunities, and then it lists all of my
08:41:19 23 manuscripts and abstracts.

08:41:22 24 Q Does Plaintiffs' Exhibit 1161 accurately summarize your
08:41:26 25 professional and educational background?

08:41:28 1 A Yes.

08:41:30 2 MR. M. KENNEDY: Your Honor, we would like to
08:41:31 3 admit Plaintiffs' Exhibit 1161 into evidence.

08:41:34 4 MR KLEIN: No objection.

08:41:35 5 THE COURT: 1161 is admitted.

08:41:35 6 (Plaintiffs' Exhibit 1161 received in
08:41:35 7 evidence.)

08:41:35 7 BY MR. M. KENNEDY

08:41:38 8 Q Dr. Budoff, have you worked with us to prepare slides to
08:41:42 9 aid your testimony today?

08:41:43 10 A Yes.

08:41:44 11 Q Or I should say to illustrate your testimony today?

08:41:47 12 Have you prepared one such slide that summarizes
08:41:50 13 your educational qualifications?

08:41:53 14 A Yes.

08:41:53 15 MR. M. KENNEDY: Mr. Brooks, if we could have
08:41:56 16 PDX 2-2.

08:41:56 17 BY MR. M. KENNEDY:

08:41:58 18 Q And, Dr. Budoff, is this that slide?

08:42:01 19 A Yes.

08:42:01 20 Q Could we focus on the last two items on this slide
08:42:06 21 starting with the internship and residency in internal
08:42:10 22 medicine. Could you describe what that involved.

08:42:12 23 A Yes. So, my internship and residency is three years of
08:42:20 24 training to become an internist or a primary care physician.

08:42:23 25 So I spent three years at Harbor UCLA Medical Center

08:42:28 1 affiliated with UCLA School of Medicine under that training.

08:42:33 2 Q What does it mean -- what does doing an internship in
08:42:36 3 this context involve?

08:42:37 4 A So it's basically on-call every third or fourth night,
08:42:42 5 taking care of patients in the hospital, seeing patients in
08:42:45 6 clinic, just basically learning how to practice general
08:42:49 7 medicine.

08:42:50 8 Q I would like to move to the cardiology fellowship at
08:42:54 9 Harbor UCLA Medical Center. What it did that involve?

08:42:58 10 A So that's another three years of commitment. This is
08:43:00 11 just focused on learning how to be a cardiologist, so I'm
08:43:04 12 specializing in cardiovascular medicine and learning all of
08:43:08 13 the aspects, including imaging and how to treat patients and
08:43:13 14 how to do the invasive procedures.

08:43:15 15 Q And so am I correct that starting in 1997 or so you were
08:43:18 16 a full-fledged cardiologist?

08:43:20 17 A Yes.

08:43:20 18 Q So you testified that you're a professor of medicine.
08:43:27 19 What are your responsibilities in that role?

08:43:29 20 A So my primary responsibilities as a professor of medicine
08:43:33 21 is to teach and do research. There's still an adage of
08:43:38 22 publish or perish, so I still publish quite a bit as far as my
08:43:41 23 academic career.

08:43:42 24 But I spend most of my time teaching, and I'll teach
08:43:46 25 everybody from the primary care specialists, family medicine

08:43:50 1 doctors, and internal medicine doctors, the cardiology
08:43:56 2 fellows, the interns and residents, and then the medical
08:43:59 3 students who are also rotating through different rotations
08:44:02 4 with me.

08:44:03 5 Q How long have you been teaching?

08:44:05 6 A Oh, I became a -- I started my professorship series in
08:44:09 7 1997 so I've been teaching full time since July 1997.

08:44:14 8 Q And am I correct that you teach practicing physicians?

08:44:17 9 A Yes.

08:44:17 10 Q Could you go into a little more detail about what you
08:44:21 11 teach them.

08:44:22 12 A Yeah. So I spend a lot of time -- I get invited to a lot
08:44:27 13 of different academic meetings, so I'll present at large scale
08:44:31 14 meetings where there will be anywhere from dozens to hundreds
08:44:35 15 of practicing physicians, and I will give lectures on --
08:44:38 16 usually on things related to lipids or things related to
08:44:44 17 cardiovascular imaging to these different groups.

08:44:47 18 Q Do you have an understanding of why people ask you to do
08:44:51 19 these lectures?

08:44:52 20 A Well, I've been told that I'm fairly clear when I
08:44:56 21 lecture, and they find it educational so they invite me back.
08:45:01 22 So I usually end up doing these on a regular basis.

08:45:04 23 Q Are you involved in any other physician education
08:45:07 24 activities we haven't already covered?

08:45:09 25 A Well, I do a lot of publishing, and some of that is in

08:45:14 1 the form of guidelines. So I'll publish medical guidelines
08:45:18 2 I'll write on behalf of different societies, different
08:45:22 3 guidelines to help educate physicians in the field on how to
08:45:26 4 practice cardiology or how to use certain tools in their
08:45:31 5 practice.

08:45:32 6 Q What drew you to preventive cardiology?

08:45:36 7 A Yeah, so, I mean, the long-standing relationships with
08:45:40 8 the patient, the ability to try to help them, enable them to
08:45:45 9 prevent a catastrophic event was very rewarding for me, and
08:45:49 10 I've enjoyed it in my clinical practice, so I've stayed with
08:45:53 11 it over the many years since I started.

08:45:56 12 Q You mentioned you conduct research. What kind of
08:45:59 13 research do you conduct?

08:46:00 14 A Yeah, so most of my research revolves around looking at
08:46:04 15 the effect of different therapies on atherosclerosis, plaque
08:46:14 16 build-up in the arteries, to see if drug X improves the
08:46:16 17 arteries or if drug Y causes more problems in the arteries.

08:46:18 18 I also do a lot of research on clinical trials so
08:46:22 19 I'll work with other investigators to perform clinical studies
08:46:27 20 to see if a drug has its desired affect, be it anything from
08:46:32 21 lowering the blood pressure to improving the cholesterol
08:46:37 22 panel, to improving the triglycerides.

08:46:37 23 Q What is an investigator in the context of clinical
08:46:40 24 trials?

08:46:40 25 A Yeah, so an investigator is the person who is principally

08:46:43 1 responsible for the local site, and the primary investigator
08:46:49 2 or the principal investigator is responsible for the overall
08:46:53 3 performance of the trial, everything from making sure the
08:46:55 4 patients stay in the study and are appropriately treated, to
08:46:59 5 ensuring their safety, and then to make sure that we capture
08:47:02 6 all of the desired endpoints so that the trial can be
08:47:06 7 published and hopefully advance science.

08:47:09 8 Q How long have you -- or how many times have you been a
08:47:12 9 principal investigator at the national level?

08:47:14 10 A Probably around a dozen or so.

08:47:18 11 Q How many times have you been the principal investigator
08:47:21 12 on a clinical trial at a local site?

08:47:24 13 A Oh, probably about a hundred times.

08:47:27 14 Q Can you give a few examples of clinical studies you've
08:47:32 15 been involved in recently?

08:47:33 16 A Yes, I'm currently performing a multicenter trial that
08:47:36 17 I'm the overall principal investigator on called EVAPORATE.
08:47:39 18 That's actually using the product in question here, Vascepa,
08:47:44 19 to look at plaque over time.

08:47:46 20 So I'm in charge of all of the sites in the trial
08:47:48 21 and the overall performance of the trial, and I recently
08:47:52 22 presented some of the interim data at the largest meeting of
08:47:56 23 cardiology in the United States called the American Heart
08:47:58 24 Association Meeting on a very large scale.

08:48:02 25 Q What do you hope to show in the EVAPORATE trial?

08:48:06 1 A So EVAPORATE is -- the target of EVAPORATE is to
08:48:10 2 demonstrate whether Vascepa reduces plaque in the coronary
08:48:15 3 arteries as compared to placebo, so to see if some of its
08:48:19 4 cardiovascular benefits that we've seen in the REDUCE-IT trial
08:48:23 5 actually translate into plaque reduction at the coronary
08:48:28 6 level.

08:48:28 7 Q Can you tell us how EVAPORATE is going so far?

08:48:31 8 A Yeah. It concludes in February. Hopefully by the end of
08:48:35 9 the February we'll have our last patient, last visit.

08:48:38 10 So hopefully we'll be -- we plan on presenting this
08:48:40 11 at the European Society of Cardiology Meeting in July or
08:48:44 12 August which is the largest meeting in the world of
08:48:47 13 cardiologists.

08:48:48 14 Q Why do you do so many clinical trials?

08:48:51 15 A Well, clinical trials have, I feel, a great purpose. We
08:48:55 16 have to remember that about half of what we discover in -- at
08:48:59 17 least in fields like cardiology, are based on these clinical
08:49:04 18 trials.

08:49:04 19 These clinical trials show us whether a drug works
08:49:08 20 and in whom they work. So, for example, if we just go back to
08:49:11 21 the REDUCE-IT trial, it affords us a great opportunity to
08:49:14 22 understand that we can reduce cardiovascular events in
08:49:19 23 patients who have certain clinical criteria. So participating
08:49:24 24 in those studies help us treat patients better.

08:49:26 25 Q You mentioned REDUCE-IT. Did you have a role in the

08:49:29 1 REDUCE-IT clinical trials?

08:49:30 2 A Yeah, I was local principal investigator so I was
08:49:33 3 responsible for my local site, and then I was a co-author on
08:49:37 4 one of the recent papers describing the results in the United
08:49:40 5 States population of REDUCE-IT.

08:49:41 6 Q So I think you mentioned earlier that you publish so that
08:49:44 7 you don't perish. Have you prepared a slide that lists some
08:49:49 8 of your publications?

08:49:50 9 A Yes.

08:49:51 10 MR. M. KENNEDY: Mr. Brooks, can we please have
08:49:52 11 PDX 2-3.

08:49:52 12 BY MR. M. KENNEDY:

08:49:56 13 Q And are these some selected publications from your
08:50:00 14 curriculum vitae, PX 11671?

08:50:04 15 A Yes.

08:50:04 16 Q Could you tell us a little bit more about number 1103.
08:50:09 17 Is that the paper about REDUCE-IT that you just mentioned?

08:50:12 18 A Yes. So it's very important to understand how the U.S.
08:50:17 19 population behaves in a clinical trial. Sometimes it's a
08:50:20 20 little bit different than the overall clinical trials that are
08:50:24 21 done with a worldwide influence.

08:50:26 22 So Dr. Bhatt and I put together this paper to look
08:50:32 23 at the results of the -- of the 3,000 plus patients who were
08:50:37 24 United States participants in the trial to see how they
08:50:40 25 performed.

08:50:40 1 Q And if you could tell us a little bit more about 783. Is
08:50:44 2 that also related to EPA?

08:50:46 3 A Yes. This was a review article. As I was preparing my
08:50:52 4 research and preparing for the EVAPORATE trial to see how we
08:50:57 5 wanted to perform that study and writing it up, we came across
08:51:01 6 a lot of information related to the effects of both EPA and
08:51:05 7 DHA on lipoproteins on lipids. So we wrote a little review
08:51:12 8 article to help clarify that part of the science.

08:51:14 9 Q Who is the intended audience for these publications that
08:51:21 10 you author?

08:51:22 11 A Yeah, so, generally, it depends on where we publish it.
08:51:27 12 For example, the first publication that we discussed was
08:51:30 13 published in *Circulation*. That's the Journal of the American
08:51:34 14 Heart Association, so it generally goes out to all
08:51:37 15 cardiologists in the United States and obviously has a bigger
08:51:42 16 circulation than just the U.S. It goes around to
08:51:46 17 cardiologists in the world. So that paper was more focused on
08:51:50 18 getting the word out to cardiology.

08:51:50 19 Q So I would like to ask you a few more questions about
08:51:53 20 your clinical practice. How long have you been seeing
08:51:56 21 patients?

08:51:56 22 A I've been seeing patients since 1990 when I started my
08:52:01 23 internship. We had what's called a continuity clinic, and I
08:52:05 24 would see patients in my clinic starting in 1990, and I've
08:52:09 25 continued since then.

08:52:10 1 Q How many patients do you see in a typical month?

08:52:13 2 A So I see approximately 200 patients in different venues.

08:52:19 3 Q Are there -- do you have different -- do you have
08:52:23 4 different places where you practice?

08:52:24 5 A Yes, and it depends on my rotations at the time. For
08:52:30 6 example, right now I'm supposed to be in the intensive care
08:52:33 7 unit, in the cardiac care unit. So tomorrow morning I will be
08:52:37 8 rounding in the CCU and taking care of more acute patients.

08:52:41 9 I also have a private clinic where I see my own
08:52:44 10 patients. And I supervise fellows as well in the cardiology
08:52:48 11 clinic where they will see a patient, and then I will go
08:52:52 12 discuss the patient with them, go in and discuss the case with
08:52:55 13 the patient, and see the patient as -- in a more supervisory
08:52:59 14 role.

08:53:00 15 Q Now, in your own practice how do those patients find you?

08:53:03 16 A Yeah, I have a pretty typical preventive cardiology
08:53:08 17 practice. My practice entails getting referrals from primary
08:53:12 18 care physicians.

08:53:13 19 So a doctor may see somebody with high
08:53:16 20 triglycerides, or may see somebody with very high LDL
08:53:20 21 cholesterol, or a bad family history of heart disease and
08:53:23 22 refer them directly to me, or I get patients directly from
08:53:28 23 word of mouth. Some patients, some of my patients refer me,
08:53:32 24 and their colleagues or friends or family members will come to
08:53:36 25 see me as well.

08:53:37 1 Q What are the common medical problems that patients face
08:53:40 2 in your practice?

08:53:41 3 A Yeah. So my private practice, it's fairly focused on
08:53:45 4 preventive cardiology. So, in other words, I try to take
08:53:47 5 patients who are high risk and try to work with them on risk
08:53:51 6 reduction. So that could be anything from diet and exercise
08:53:54 7 to drug therapy, to other types of interventions to help
08:53:59 8 prevent them from ever suffering a cardiovascular event.

08:54:04 9 Q Do you see patients with elevated triglyceride levels?

08:54:07 10 A Yes.

08:54:07 11 Q How often?

08:54:08 12 A Very frequently. Elevated triglyceride levels are part
08:54:12 13 of a mixed dyslipidemia, so they're part of -- people come in
08:54:18 14 with high cholesterol and high triglycerides, and then I also
08:54:21 15 see patients with isolated high triglycerides.

08:54:25 16 Q Do you see patients with severe hypertriglyceridemia?

08:54:29 17 A Yes.

08:54:30 18 Q How often?

08:54:31 19 A So it's a less common disease. I don't have a lipid
08:54:35 20 clinic, I have a general preventive cardiology clinic, but I
08:54:38 21 do see patients regularly with severe hypertriglyceridemia.

08:54:44 22 Q Do you see patients with elevated LDL-C levels?

08:54:46 23 A Yes.

08:54:46 24 Q How often?

08:54:46 25 A So that's most the common disorder that I see and the

08:54:50 1 most common disorder that I treat.

08:54:52 2 And, again, those patients with elevated LDL, or bad
08:54:57 3 cholesterol, oftentimes have abnormal triglycerides as well.

08:55:01 4 So we call that a mixed dyslipidemia.

08:55:04 5 Q Beyond your teaching, research, and clinical obligations,
08:55:09 6 do you engage in other professional activities?

08:55:11 7 A Yes.

08:55:12 8 MR. M. KENNEDY: Mr. Brooks, could we please
08:55:14 9 have slide PDX 2-4.

08:55:14 10 BY MR. M. KENNEDY:

08:55:18 11 Q And can you just briefly explain what you've depicted on
08:55:21 12 this slide.

08:55:21 13 A Yeah, so these is just some of my recent memberships or,
08:55:25 14 rather, affiliations with large organizations, national or
08:55:29 15 international organizations, where my expertise was -- I was
08:55:34 16 asked to be on the executive committee or be the chair of the
08:55:38 17 steering committee for different groups.

08:55:41 18 Q Have you ever received any awards from your peers?

08:55:44 19 A Yes.

08:55:46 20 MR. M. KENNEDY: Mr. Brooks, can we please have
08:55:50 21 PDX 2-5.

08:55:50 22 BY MR. M. KENNEDY:

08:55:52 23 Q Are these some of the awards that you've received that
08:55:54 24 are reflected in your curriculum vitae?

08:55:57 25 A Yes.

08:55:58 1 Q Could you tell us about one of these awards that may be
08:56:01 2 particularly meaningful to you.

08:56:02 3 A Yeah, the one that's bolded is, I think, the most
08:56:06 4 prestigious is to be named an Endowed Chair.

08:56:09 5 That comes with some financial support because
08:56:12 6 there's an endowment that supports your position, but, also,
08:56:16 7 more importantly, you're recognized among your peers as being
08:56:19 8 at the highest level of that field.

08:56:21 9 So this is the Endowed Chair of Preventive
08:56:24 10 Cardiology that I was awarded in 2015.

08:56:29 11 MR. M. KENNEDY: Your Honor, at this time Amarin
08:56:31 12 offers Dr. Budoff as an expert in the clinical treatment of
08:56:35 13 patients with lipid disorders, including severe
08:56:42 14 hypertriglyceridemia, and as an expert in cardiology.

08:56:44 15 MR KLEIN: No objection.

08:56:46 16 THE COURT: The request to certify Dr. Budoff in
08:56:49 17 the clinical treatment of lipid disorders, including severe
08:56:55 18 TG, and just preventive cardiology?

08:56:59 19 MR. M. KENNEDY: Cardiology in general.

08:57:01 20 THE COURT: Cardiology in general. That request
08:57:02 21 is granted.

08:57:03 22 MR. M. KENNEDY: Thank you, Your Honor.

08:57:03 23 BY MR. M. KENNEDY:

08:57:05 24 Q So, Dr. Budoff, just to orient ourselves, I would like to
08:57:08 25 go over a little bit of scientific background. I know some of

08:57:12 1 this was covered yesterday.

08:57:14 2 MR. M. KENNEDY: Mr. Brooks, if we could pull up
08:57:16 3 slide PDX 2-6.

08:57:16 4 BY MR. M. KENNEDY:

08:57:19 5 Q So, Dr. Budoff, what have you shown on this slide?

08:57:21 6 A Yeah, so this is a lipoprotein. A lipoprotein -- I know
08:57:26 7 Dr. Ketchum touched on this yesterday, but a lipoprotein is a
08:57:31 8 kind of a way that we transport both cholesterol and
08:57:36 9 triglycerides around the body.

08:57:38 10 If they are heavily containing both cholesterol
08:57:43 11 and/or triglycerides, the bad lipoproteins, they're designated
08:57:48 12 as apolipoprotein B, so you can see that in purple. And you
08:57:52 13 can see within the content of that lipoprotein, that bad
08:57:57 14 lipoprotein, that has both cholesterol in yellow and
08:58:01 15 triglycerides depicted in red.

08:58:03 16 Q What are triglycerides?

08:58:05 17 A So triglycerides are basically how we store energy and
08:58:09 18 how we then given energy to different organs when needed.

08:58:13 19 Q Are more triglycerides better?

08:58:15 20 A Well, up to a point. We need triglycerides, they are an
08:58:19 21 energy source, but most commonly, especially in the United
08:58:23 22 States, we have excess. We -- we have too many -- we eat too
08:58:28 23 many calories, we store that as triglycerides, and
08:58:32 24 triglycerides then build-up in the bloodstream which can cause
08:58:37 25 plaque build-up, blockages in the arteries that then

08:58:40 1 subsequently cause heart attacks and death.

08:58:42 2 Q What purpose does cholesterol serve?

08:58:45 3 A Cholesterol is very important. It's a precursor for
08:58:49 4 vitamins as well as for hormones, so it's a very important
08:58:52 5 precursor.

08:58:54 6 But, again, in the United States we tend to run an
08:58:56 7 excess of cholesterol, and that can, again, start to block up
08:58:59 8 the arteries, gets converted into malignant cells that can
08:59:04 9 then cause plaque buildup and heart attacks and strokes.

08:59:09 10 Q And what purpose does apolipoprotein B serve?

08:59:11 11 A So the apolipoproteins are divided into the good, those
08:59:17 12 apo A, and bad lipoproteins, the ones that contain lot of
08:59:21 13 cholesterol and triglyceride, are designated apo B.

08:59:25 14 So apo B -- I think of B as bad, so apo B is the bad
08:59:29 15 lipoprotein that, when in excess, carries around too many
08:59:33 16 triglycerides and cholesterol and can cause excess heart
08:59:36 17 attacks, strokes, and death.

08:59:38 18 MR. M. KENNEDY: Mr. Brooks, can we have

08:59:43 19 PDX 2-7.

08:59:43 20 BY MR. M. KENNEDY:

08:59:44 21 Q Dr. Budoff, what have you shown on this slide?

08:59:46 22 A Yeah, so this is just showing the natural -- the natural
08:59:52 23 progression of what happens to the lipoproteins in our body.

08:59:57 24 When the liver first processes the food and creates
09:00:00 25 these very low-density lipoproteins, they are very rich in

09:00:06 1 triglycerides. Then, via lipoprotein lipase and other
09:00:13 2 enzymes, we deliver some of the triglycerides to organs.

09:00:16 3 And the lipoprotein gets smaller and denser, so it
09:00:21 4 goes from very low-density to intermediate density. It's now
09:00:26 5 a smaller lipoprotein, has less triglycerides and relatively
09:00:30 6 more cholesterol, because the cholesterol is still there, and
09:00:33 7 then further delivered to LDL cholesterol.

09:00:38 8 LDL cholesterol is what we commonly call bad
09:00:42 9 cholesterol. This is a cholesterol-rich particle that is most
09:00:47 10 associated with heart attacks and strokes and of great concern
09:00:52 11 when we think about a patient's cardiovascular risk if they
09:00:56 12 have too much LDL cholesterol.

09:00:59 13 Q Again, something we covered a little bit yesterday, but
09:01:03 14 what is hypertriglyceridemia?

09:01:06 15 A So hypertriglyceridemia is simply hyper, too much,
09:01:10 16 triglycerides, and then emia is in the blood. So too many
09:01:14 17 triglycerides in the blood, and, again, that's what we call
09:01:17 18 atherogenic. It causes atherosclerosis, and it causes
09:01:23 19 cardiovascular events.

09:01:25 20 Q And what is severe hypertriglyceridemia, which I may also
09:01:29 21 refer to STG?

09:01:30 22 A So severe hypertriglyceridemia is a less common disorder.
09:01:35 23 It's an extreme state of hypertriglyceridemia mostly caused by
09:01:40 24 genetics, so we know it as a chronic condition that is
09:01:45 25 lifelong.

09:01:46 1 And when the triglycerides are very high, there are
09:01:49 2 different risks as compared to when the triglycerides are only
09:01:52 3 moderately elevated.

09:01:54 4 Q Is severe hypertriglyceridemia a condition recognized in
09:01:59 5 medical literature?

09:02:00 6 A Yes.

09:02:01 7 Q Could you give me example of the type of medical
09:02:04 8 literature in which it's recognized?

09:02:05 9 A Yes, so it's been discussed in the cholesterol
09:02:07 10 guidelines, guidelines that talk about lipids and how to treat
09:02:12 11 lipids, for decades.

09:02:13 12 Q Now, you've mentioned guidelines a couple times. What
09:02:16 13 are guidelines in this context?

09:02:17 14 A So guidelines are very simply the -- to establish the
09:02:21 15 medical standard of care. So they instruct clinicians who are
09:02:26 16 practicing in the field on the best practices and what they
09:02:30 17 should do when encompassing a certain condition.

09:02:33 18 Q Do you use medical guidelines in your own practice?

09:02:36 19 A Yes, every day.

09:02:37 20 Q Do you have experience writing guidelines?

09:02:39 21 A Yes. I've been involved in probably around 13 or 14
09:02:43 22 guidelines, sometimes as the first author, sometimes as a
09:02:47 23 member of the writing group.

09:02:49 24 MR. M. KENNEDY: Mr. Brooks, could we have
09:02:51 25 Plaintiffs' Exhibit 989.

09:02:53 1 And, Your Honor, I believe this is one the
09:02:55 2 exhibits that has already been preadmitted in this case.

09:02:55 3 BY MR. M. KENNEDY:

09:03:01 4 Q Dr. Budoff, do you recognize this document?

09:03:03 5 A Yes.

09:03:04 6 Q What is it?

09:03:04 7 A So this is a cholesterol guideline. We commonly refer to
09:03:09 8 it as the Adult Treatment Panel III or ATP III report.

09:03:16 9 Q What role does the American Heart Association have in
09:03:19 10 these guidelines? I see that this document has its logo on
09:03:24 11 it.

09:03:24 12 A Yes, so this is -- this is a primary -- they are one the
09:03:29 13 primary writers of the guidelines and sponsors of the
09:03:33 14 guidelines. They are signed off by many organizations, but
09:03:37 15 they are co-led by the American Heart Association and often
09:03:41 16 the American College of Cardiology.

09:03:44 17 Q What role does the ATP III guideline play in medical
09:03:48 18 practice?

09:03:48 19 A Yeah, so this was a very widely used and established
09:03:52 20 guideline in the field. It really helped us -- directed
09:03:57 21 physicians to be very aggressive with LDL or bad cholesterol
09:04:01 22 control, and it also helped define some of the treatments and
09:04:05 23 definitions of hypertriglyceridemia.

09:04:10 24 MR. M. KENNEDY: Mr. Brooks, could we go to
09:04:12 25 page 190 of this exhibit, PX 989. Also try page 33 -- yep,

09:04:21 1 there we go. If we could look at the table on the left-hand
09:04:25 2 side.

09:04:25 3 BY MR. M. KENNEDY:

09:04:27 4 Q So, Dr. Budoff, what does this table show?

09:04:30 5 A So this table demonstrates the guidelines,
09:04:36 6 recommendations for how we would categorize triglycerides.
09:04:40 7 These are still used today and have been republished in many
09:04:44 8 guidelines since 2002 when the ATP III came out.

09:04:58 9 You can see normal triglycerides is considered less
09:04:59 10 than 150 milligrams per deciliter, so we are looking at
09:05:00 11 concentrations of triglycerides in the blood, and these are
09:05:03 12 always taken in the fasting state.

09:05:05 13 And then you can see borderline high triglycerides
09:05:10 14 goes up to 199, high triglycerides are over 200 up to 499, and
09:05:15 15 then very high triglycerides, which we also now call severe
09:05:20 16 hypertriglyceridemia, is defined as greater than or equal to
09:05:25 17 500 milligrams per deciliter.

09:05:26 18 Q You mentioned something about the fasting state. Why is
09:05:30 19 it important to test triglyceride levels in the fasting state?

09:05:34 20 A Yeah, so triglycerides can vary throughout the day and
09:05:38 21 can vary based on our diet. So there are small changes from
09:05:43 22 hour to hour. And if we had a fatty meal or a high
09:05:46 23 carbohydrate meal, our triglycerides may go up a little bit,
09:05:51 24 so there are variabilities.

09:05:54 25 So to accurately assess a patient's baseline, where

09:05:57 1 they're starting with their triglyceride, we do it in the
09:06:01 2 fasting state so after I treat a patient, be it with diet and
09:06:06 3 exercise, or be it with a drug, I can then follow that value
09:06:09 4 in the fasting state to see what the net effect was of my
09:06:13 5 treatment.

09:06:13 6 Q Are these classifications still used by clinicians today
09:06:17 7 in 2020?

09:06:18 8 A Yes, these are the -- to my knowledge, the only commonly
09:06:21 9 used classifications for hypertriglyceridemia.

09:06:25 10 Q Now, do you treat patients differently depending on which
09:06:28 11 category of triglyceride level they fall into?

09:06:40 12 A Yes.

09:06:41 13 MR. M. KENNEDY: Mr. Brooks, could we please
09:06:41 14 have PDX 2-8.

09:06:41 15 BY MR. M. KENNEDY:

09:06:44 16 Q Dr. Budoff, what does this slide depict?

09:06:44 17 A Yes, so this is based on -- you can see the ATP III are
09:06:50 18 recommendations, that's the reference at the bottom or the
09:06:51 19 source at the bottom.

09:06:53 20 And it basically breaks up the groups into high
09:06:56 21 triglycerides, what are described here as 200 to 499, and then
09:07:01 22 very high or severe hypertriglyceridemia, which is greater
09:07:05 23 than 500 milligrams per deciliter at the top.

09:07:08 24 Q So a patient has a baseline fasting triglyceride level
09:07:14 25 over 500, am I correct your primary concern at that point is

09:07:18 1 pancreatitis?

09:07:19 2 A Yes.

09:07:20 3 Q What is pancreatitis?

09:07:22 4 A So pancreatitis, as was described yesterday, is a severe
09:07:27 5 life-threatening condition where the pancreatic enzymes -- the
09:07:32 6 pancreas creates enzymes that are supposed to digest food.

09:07:37 7 If they have too many triglycerides, and the
09:07:39 8 triglycerides block up the ducts, and the pancreas can't
09:07:40 9 perform properly, those enzymes can leak out, dissolve the
09:07:45 10 pancreas itself, that's inflammation of the pancreas, thus the
09:07:49 11 term pancreatitis, and can also actually get into the
09:07:53 12 abdominal cavity and cause much more problems.

09:07:56 13 Q Does the patient's LDL-C level affect their treatment?

09:08:01 14 A Yes.

09:08:01 15 Q How so?

09:08:02 16 A Well, so our first concern when the triglycerides are
09:08:07 17 above 500 is pancreatitis because this is an acute, short-term
09:08:12 18 life threatening illness. So pancreatitis can kill somebody
09:08:19 19 fairly quickly, so we want to get the triglycerides below and
09:08:23 20 maintain them below 500.

09:08:25 21 Once we've done that and brought them down from
09:08:28 22 severe hypertriglyceridemia to -- to high triglycerides, 200
09:08:36 23 to 499, we can then further assess them to decide whether or
09:08:41 24 not they're at cardiovascular risk.

09:08:43 25 If their LDL cholesterol is elevated, if they have

09:08:48 1 diabetes, if they have other risk factors, we would then
09:08:51 2 consider further therapy such as a statin.

09:08:54 3 Q What causes severe hypertriglyceridemia?

09:08:57 4 A So hypertriglyceridemia is primarily a genetic disorder,
09:09:02 5 so we're born with it. We don't have -- we don't process --
09:09:05 6 we don't have certain enzymes, or we have deficiencies in
09:09:08 7 certain enzymes.

09:09:10 8 So when -- that original picture that I showed, when
09:09:13 9 there's the VLDL, that VLDL, that very low-density
09:09:17 10 lipoprotein, that big one, can't get brought down towards LDL
09:09:21 11 cholesterol, so it stays in the bloodstream carrying too many
09:09:26 12 triglyceride around the body, and that increases our risk of
09:09:30 13 pancreatitis.

09:09:31 14 MR. M. KENNEDY: Mr. Brooks, could we have
09:09:33 15 Plaintiffs' Exhibit 269.

09:09:33 16 BY MR. M. KENNEDY:

09:09:38 17 Q Dr. Budoff, do you recognize this document?

09:09:41 18 A Yes.

09:09:41 19 Q What is it?

09:09:42 20 A So this is another guideline by the American Heart
09:09:46 21 Association published in the same journal as ATP III,
09:09:50 22 *Circulation*, and this is a guideline specifically focusing on
09:09:56 23 triglycerides and cardiovascular disease.

09:09:59 24 Q Is this a guideline that you've used in your own
09:10:02 25 practice?

09:10:02 1 A Yes.

09:10:03 2 Q Is this a document you relied on in forming your opinions
09:10:06 3 in this case?

09:10:06 4 A Yes.

09:10:09 5 MR. M. KENNEDY: Your Honor, I would like to
09:10:10 6 enter PX 269 into evidence.

09:10:13 7 MR KLEIN: No objection.

09:10:14 8 THE COURT: 269 is admitted.

09:10:14 9 (Plaintiffs' Exhibit 269 received in
09:10:17 10 evidence.)

09:10:17 10 MR. M. KENNEDY: Mr. Brooks, could we go to the
09:10:20 11 table on page 12 of this document.

09:10:20 12 BY MR. M. KENNEDY:

09:10:25 13 Q Dr. Budoff, what does this table depict?

09:10:28 14 A So this is demonstrating the -- as the table is titled,
09:10:34 15 Causes of Very High Triglycerides That May Be Associated With
09:10:39 16 Pancreatitis.

09:10:40 17 Q And the first category appears to say Genetic. Can you
09:10:44 18 tell us a little bit more about that category.

09:10:47 19 A Yeah, so that's the largest and most common cause of very
09:10:52 20 high triglyceride, thus it's listed first.

09:10:54 21 They list the six most common genetic disorders --
09:10:59 22 seven most common genetic disorders here, but there are others
09:11:03 23 as well that are listed in the document.

09:11:06 24 There are many genetic causes of severe
09:11:10 25 hypertriglyceridemia. These are again the most common ones

09:11:14 1 that are listed in this table.

09:11:16 2 Q What's the second category on the list, Acquired
09:11:19 3 Disorders of Metabolism? What does that involve?

09:11:22 4 A Yeah, so, you know, genetic causes are lifelong, we're
09:11:27 5 born with them, they stay with us forever and require
09:11:30 6 long-term therapy.

09:11:31 7 Acquired disorders of metabolism are short-term
09:11:35 8 causes, what we call secondary causes of high triglyceride.

09:11:39 9 So, for example, one of the -- one of the things
09:11:42 10 listed here is poorly controlled diabetes. So if a person
09:11:46 11 with diabetes goes into a very high diabetic state where their
09:11:52 12 blood sugar runs really high, the triglycerides can
09:11:55 13 transiently, temporarily go high.

09:11:58 14 So we would eliminate this prior to medical therapy
09:12:02 15 for high triglycerides because the cause of their high
09:12:06 16 triglycerides is not genetics. The cause of their
09:12:09 17 triglyceride problem is diabetes. So you treat the root
09:12:13 18 cause. You would treat the diabetes and not treat the high
09:12:18 19 triglycerides first.

09:12:21 20 MR. M. KENNEDY: Your Honor, I'm advised that
09:12:23 21 there's a technical issue with defendants' screens. I was
09:12:26 22 wondering if we might take a brief break to try to fix it, if
09:12:31 23 they want to take a break.

09:12:32 24 MR KLEIN: Yes.

09:12:34 25 MR. M. KENNEDY: Okay.

09:12:34 1 THE COURT: Yes, and Miss Clerk will alert our
09:12:37 2 IT staff and see if he can help. We'll take a brief recess.

09:38:39 3 (A recess was taken.)

09:38:39 4 THE COURT: Please be seated.

09:38:39 5 How did we resolve the issue of the monitors?
09:38:43 6 Are the monitors working now?

09:38:45 7 THE CLERK: No.

09:38:45 8 MR KLEIN: They are not, but we are able to
09:38:48 9 review it on the big screen.

09:38:49 10 THE COURT: Do you have hardcopies of the
09:38:51 11 demonstratives?

09:38:52 12 MR KLEIN: We do, but the issue really is the
09:38:55 13 call-outs from the hot seat person.

09:38:59 14 MR. M. KENNEDY: Your Honor, may I proceed?

09:39:00 15 THE COURT: Yes.

09:39:00 16 BY MR. M. KENNEDY:

09:39:02 17 Q So, Dr. Budoff, let's go back to Plaintiffs' Exhibit 269,
09:39:07 18 table 5 which was on the screen when we --

09:39:09 19 THE COURT: I'm sorry, now my screen is not on.

09:39:09 20 (Discussion held off the record.)

09:39:44 21 THE COURT: Do you have an extra copy?

09:39:45 22 MR. M. KENNEDY: Of the slides, your Honor?

09:39:45 23 THE COURT: Yes.

09:39:45 24 MR. M. KENNEDY: We do.

09:39:45 25 THE COURT: Or I can my staff make a copy.

09:39:45 1 MR. M. KENNEDY: No -- although, Your Honor, I
09:39:46 2 would say we are going to be going to particular portions of
09:39:49 3 exhibits, and that's what we don't have hardcopies of is like
09:39:52 4 exactly --

09:39:52 5 THE COURT: I have the exhibits. If you
09:39:54 6 reference the exhibit number, I can pull up the exhibit
09:39:57 7 number.

09:39:57 8 MR. M. KENNEDY: I can reference exactly where
09:39:59 9 we are. I'll make sure to do that.

09:40:01 10 THE COURT: If we -- I'm not able to get the
09:40:03 11 monitor to work over the noon break, we may need to move to
09:40:07 12 the courtroom across the hall until we can get outside vendors
09:40:12 13 to come in and fix the monitors, but that's going to require
09:40:15 14 lot of changes.

09:40:16 15 MR. SIPES: Your Honor, we do have an extra copy
09:40:19 16 available of the exhibits.

09:40:19 17 THE COURT: I have the exhibits. Thank you.

09:40:21 18 MR. M. KENNEDY: Your Honor, I'll make sure to
09:40:23 19 identify precisely where we are in each exhibit.

09:40:25 20 THE COURT: Thank you.

09:40:27 21 MR. M. KENNEDY: So we're currently at
09:40:30 22 Plaintiffs' Exhibit 269, table 5. Your Honor, that's in PX
09:41:00 23 269, that's page 2302.

09:41:08 24 THE COURT: 2302. If you'll give me one minute,
09:41:15 25 let me pull up the exhibit. So, it's Exhibit 269.

09:41:24 1 THE CLERK: Your Honor, I'm going to try a small
09:41:28 2 experiment and hopefully everything won't crash.

09:41:54 3 THE COURT: All right, 269.

09:41:56 4 MR. M. KENNEDY: Yeah, the pagination on the top
09:41:58 5 left is 2302. There's also pagination associated with the
09:42:02 6 exhibit number, and that's 12.

09:42:03 7 THE COURT: Thank you. You just need to give me
09:42:08 8 the pagination associated with the exhibit number.

09:42:11 9 MR. M. KENNEDY: Understood, Your Honor.

09:42:22 10 THE COURT: I have it. Thank you.

09:42:22 11 BY MR. M. KENNEDY:

09:42:23 12 Q So, Dr. Budoff, we've been discussing the causes of very
09:42:27 13 high triglycerides that are listed on PX 269, the guidelines.

09:42:31 14 Let's turn to the third category listed here which
09:42:34 15 is Drugs (medications). How can medications cause severe
09:42:40 16 hypertriglyceridemia?

09:42:41 17 A Yeah, so patients who already have a predisposition,
09:42:44 18 already have high triglycerides, they're in the high
09:42:47 19 triglycerides category, if they go on certain drugs, could
09:42:51 20 push them up into the very high triglyceride category.

09:42:54 21 So it would be what we would say exacerbates or
09:42:57 22 makes worse their underlying condition. So these are -- these
09:43:00 23 are a list of the most common drugs that are associated with
09:43:04 24 elevations in triglycerides.

09:43:05 25 Q And then the fourth category here it says Diet. How does

09:43:12 1 diet cause very high triglycerides?

09:43:14 2 A Yeah, so diet, very similar to drugs, can make worse an
09:43:20 3 underlying disorder.

09:43:22 4 So patients who already have a problem with
09:43:25 5 triglyceride metabolism, if they have too much alcohol, if
09:43:32 6 they have a very bad diet, imagine somebody may be going from
09:43:37 7 buffet to buffet eating too much, drinking too much, that
09:43:42 8 could make worse an underlying condition.

09:43:44 9 But I just want to make it clear that if we were to
09:43:48 10 do blood draws of most of the people who are eating too much
09:43:51 11 and drinking too much at any given moment, very, very few of
09:43:55 12 them would have severe hypertriglyceridemia.

09:43:58 13 This is not a common cause of severe
09:44:00 14 hypertriglyceridemia, and, certainly, if you don't have an
09:44:04 15 underlying problem, you don't get to that level. This is a
09:44:07 16 very unusual state to see in clinical medicine.

09:44:12 17 Q So in your years of treating patients with lipid
09:44:15 18 disorders, how often would you say that you see a patient who
09:44:19 19 has very high triglycerides solely because of diet?

09:44:22 20 A Yeah, so that would be extremely rare. That would
09:44:27 21 invoke -- once I corrected their diet, their triglycerides
09:44:30 22 came down to 150 or below, came back down to normal, and I've
09:44:35 23 never seen that happen.

09:44:35 24 I've seen patients who have gone from very high to
09:44:39 25 high, so they've come down by 10 or 20 percent, but I've not

1 seen a three or four-fold reduction in triglycerides just by
2 improving diet.

3 Q So a new patient walks into your office, has very high
4 triglycerides, what's your first step in trying to treat them?

5 A Yeah, so my first step is always to assess what their
6 current state of health is. So I would start with just simple
7 questions about their current diet, how much alcohol they're
8 drinking, do they exercise.

9 Then I would find out about some of these reversible
10 causes of high triglycerides such as thyroid disease and
11 diabetes.

12 And when I've eliminated all of those, let's say I
13 have somebody who is already a good healthy patient, they're
14 already eating well, then I would consider starting a lipid
15 lowering therapy.

16 Q So if you've eliminated what you call reversible causes,
17 and you've determined that the patient has very high
18 triglycerides, what -- what's the next step?

19 A Right. So I counsel them on diet.

20 Unfortunately, most of us in clinical practice do
21 not have dieticians associated with our practice. The
22 healthcare system just does not support that. We just don't
23 have the resources, and we don't get reimbursed for those
24 visits. So I don't have a dietitian in my office.

25 I see the patient. I counsel them on diet and

09:46:07 1 exercise. I send them to resources to help them achieve a
09:46:11 2 good diet and exercise assuming that they're already not doing
09:46:16 3 something well.

09:46:17 4 And then, if they're not on a good diet and
09:46:20 5 exercise, I would see them back in a few months to assess how
09:46:24 6 well diet and exercise worked.

09:46:27 7 If they're already on an exceptional diet, which a
09:46:30 8 lot of my patients who come to see me are already on a good
09:46:33 9 diet, then I might start therapy at that time.

09:46:36 10 Q By therapy you mean medication.

09:46:38 11 A Yes.

09:46:39 12 Q What kind -- what medications have you used in your
09:46:41 13 career to treat very high triglycerides?

09:46:44 14 A Yeah, so there are a few that -- that we've used
09:46:48 15 commonly. Fibrates were the most commonly used historically,
09:46:55 16 then Lovaza came out, and then finally now Vascepa is
09:46:59 17 available.

09:46:59 18 Q So let's take these one at the time. What are fibrates?

09:47:03 19 A So fibrates are a therapy that specifically were designed
09:47:11 20 to lower triglycerides so they've been around for decades. To
09:47:15 21 my knowledge, all of them are now generic although there's a
09:47:19 22 new one in development.

09:47:20 23 But they basically lower triglycerides dramatically.
09:47:24 24 We get about a 50 percent reduction in triglycerides. So 600
09:47:29 25 will go to 300 when you institute an fibrate on average.

09:47:33 1 Q So do fibrates have downsides?

09:47:36 2 A Yes. Unfortunately, the downside of fibrates is while
09:47:39 3 the triglycerides come down dramatically, the bad cholesterol,
09:47:44 4 the LDL cholesterol, goes up dramatically.

09:47:48 5 So literally we get a 50 percent drop in
09:47:52 6 triglycerides, and on average in that population we get a
09:47:55 7 50 percent rise in bad cholesterol. So you're basically
09:47:59 8 trading one problem for another.

09:48:01 9 Q So do you have medications available that could address
09:48:04 10 the LDL-C rise?

09:48:07 11 A Yes.

09:48:07 12 Q Like what?

09:48:08 13 A So, at least up until 2016, if I put somebody on a
09:48:16 14 fibrate, let's say, and their triglycerides came down but
09:48:19 15 their LDL went up, let's say from 100 to 150, so now they're
09:48:24 16 at a very high risk of having a heart attack because their bad
09:48:28 17 cholesterol is high, I would then have to institute a statin
09:48:32 18 to lower that LDL by 50 percent back down to a hundred.

09:48:36 19 So I would have to use a high potency statin to
09:48:39 20 counteract a side effect of fibrates, which is something that
09:48:43 21 we always try to avoid in medicine, because now I'm putting
09:48:47 22 them on two drugs instead of one.

09:48:49 23 Q Can you characterize how often you describe fibrates to
09:48:55 24 STG patients earlier in your career compared to now.

09:48:58 25 A Yeah, so earlier in my career they were the primary

09:49:01 1 treatment of severe hypertriglyceridemia in my practice. They
09:49:05 2 were widely used, and they were, again, generally -- there
09:49:09 3 were generic versions of them so they were low cost, so I used
09:49:13 4 them quite widely.

09:49:14 5 After 2016, the Food and Drug Administration opined
09:49:18 6 that you cannot use a fibrate and a statin together.

09:49:22 7 So now I can't use fibrates in most cases of severe
09:49:27 8 hypertriglyceridemia because, if I get that 50 percent rise in
09:49:30 9 LDL, I then lose my primary way of reducing it.

09:49:34 10 Q But when you do prescribe fibrates to a patient with STG,
09:49:39 11 for how long did you prescribe them?

09:49:41 12 A So I would put them on a therapy for life, and with all
09:49:47 13 of our chronic conditions, high cholesterol, high blood
09:49:51 14 pressure, high triglycerides, those are chronic conditions,
09:49:55 15 those are lifetime treatment.

09:49:57 16 Q So I think you mentioned Lovaza. What is Lovaza?

09:50:01 17 A Lovaza is a fish oil derivative. We heard a little bit
09:50:05 18 about it yesterday. It is a mixture of EPA and DHA.

09:50:12 19 Q What -- does it lower triglycerides, and to what extent?

09:50:16 20 A Yeah. So it's another dramatic reduction of
09:50:21 21 triglycerides. Triglycerides come down by 50 percent. So
09:50:26 22 literally we see a 50 percent drop in triglycerides on average
09:50:31 23 when we put a patient with severe hypertriglyceridemia on
09:50:35 24 Lovaza therapy.

09:50:36 25 Q Is there anything wrong with Lovaza?

09:50:38 1 A Yeah, Lovaza has the exact same problem as fibrates in
09:50:44 2 that the average LDL rise, bad cholesterol rise, is
09:50:48 3 approximately 50 percent.

09:50:51 4 MR. M. KENNEDY: I would like to call up PX 566,
09:50:59 5 and, Your Honor --

09:51:00 6 THE COURT: I'm able to see it on my screen now.

09:51:03 7 MR. M. KENNEDY: Of, terrific.

09:51:03 8 BY MR. M. KENNEDY:

09:51:06 9 Q So, Dr. Budoff, what is PX 566?

09:51:11 10 A This is the package insert for Lovaza.

09:51:14 11 Q Does the package insert go by other names?

09:51:17 12 A Yes, label or package insert or prescribing information.

09:51:25 13 Q Can we use those three terms interchangeably today?

09:51:28 14 A Yes.

09:51:29 15 Q Is this label for Lovaza a document you rely on in your
09:51:33 16 own clinical practice?

09:51:35 17 A Yes.

09:51:35 18 Q Is this a document you relied on in forming your opinions
09:51:38 19 in this case?

09:51:39 20 A Yes.

09:51:40 21 MR. M. KENNEDY: Your Honor, I would like to
09:51:42 22 move PX 566 into evidence.

09:51:44 23 MR KLEIN: No objection.

09:51:45 24 THE COURT: PX 566 is admitted.

09:51:45 25

(Plaintiffs' Exhibit 566 received in evidence.)

BY MR. M. KENNEDY

Q We talked about this a little bit yesterday, but can you just explain at a high level what is the purpose of a prescribing information for an FDA approved drug?

A Yes, so this informs and instructs physicians on when to use the drug, when it's indicated, how to use the drug, and then, if you choose to use the drug, what you would expect to happen both from the positive side of things, what benefits you will get, and also what side effects or warnings you might -- you might need to be careful of when using that drug.

Q Do you use prescribing information in your own clinical practice?

A Yes.

Q How do you use it?

A So when I'm new to a drug and I'm not very, very familiar with it, I always refer to the prescribing information, and I read the prescribing information to understand the context of that drug, when I should be using it, how I should be using it, and what to look for if I choose to use it.

MR. M. KENNEDY: Mr. Brooks, could we pull up table 2 of PX 566.

BY MR. M. KENNEDY:

Q Dr. Budoff, what is the function of this portion of the Lovaza label?

09:52:59 1 A Yeah, so here you can see the randomized clinical trial.

09:53:06 2 These are how we establish what we call
09:53:08 3 evidence-based medicine. We basically do these randomized,
09:53:14 4 placebo-controlled trials. These are the highest level of
09:53:17 5 trials that can be done in clinical medicine.

09:53:20 6 And this is the trial that demonstrated the effects
09:53:22 7 of Lovaza in patients with very high triglycerides or what we
09:53:28 8 call severe hypertriglyceridemia.

09:53:30 9 Q What is Lovaza's indication?

09:53:32 10 A Lovaza is indicated to reduce triglycerides in the
09:53:36 11 setting of severe hypertriglyceridemia.

09:53:40 12 Q You mentioned the term evidence-based medicine. What is
09:53:44 13 evidence-based medicine?

09:53:45 14 A Yeah, so evidence-based medicine is basically how we look
09:53:49 15 at evidence to understand what the best science is, and then
09:53:53 16 we formulate them into manuscripts, those get incorporated
09:53:58 17 into guidelines, and those get percolated and taught to
09:54:02 18 practicing physicians.

09:54:04 19 Q Do practicing physicians practice evidence-based
09:54:07 20 medicine?

09:54:08 21 A They are supposed to.

09:54:09 22 Q Now, looking at table 2, what's your take away from the
09:54:15 23 clinical data that's shown here for Lovaza?

09:54:18 24 A Yeah, if you just look at the top line data, literally
09:54:23 25 the triglyceride results, that's our primary thing that we're

1 using it for, so that's the primary interest.

2 And you can see on the far right what the net effect
3 is if I were to put somebody on Lovaza with severe
4 hypertriglyceridemia as compared to somebody who got put on a
5 matching placebo, and you can see a 51 percent reduction in
6 their triglyceride levels.

7 Q Is there any other data here that is of particular
8 interest to you as a cardiologist?

9 A Yes, I think the most important thing -- there was two
10 things. One, if you look at the placebo category for
11 triglycerides, you see a plus 6 percent rise in triglycerides.

12 And this is very common that over time, if you don't
13 treat severe hypertriglyceridemia with a therapy, and you just
14 use diet and exercise, you do not get a net benefit, and the
15 triglycerides remain elevated. In this case, they went up by
16 7 percent.

17 Also, looking at the LDL-C at the bottom, what
18 happens to the LDL cholesterol, I mentioned that it goes up by
19 approximately 50 percent, on the far right you can see the
20 average increase was 49.3 percent.

21 So LDL went up from a baseline here in Lovaza of
22 about 90 to about 130, so they went from low risk, from a
23 cardiac perspective, to high risk because I put them on Lovaza
24 therapy.

25 Q Does that data affect your -- does that affect your

09:56:00 1 analysis in terms of whether to prescribe Lovaza to your
09:56:04 2 patients?

09:56:04 3 A Yes. I mean, this is a very serious problem.

09:56:08 4 Our number one cause of death in men and women in
09:56:11 5 the United States is heart attacks. So while pancreatitis is
09:56:16 6 a life-threatening condition that we need to treat more
09:56:19 7 acutely, heart disease is something that's more likely to
09:56:24 8 claim lives.

09:56:25 9 And if I raise somebody's LDL bad cholesterol by
09:56:30 10 50 percent, I am literally doing harm and now have to figure
09:56:34 11 out a way of counteracting that harm.

09:56:36 12 Q Is there anywhere else in the Lovaza label that discusses
09:56:39 13 the effects Lovaza has on LDL-C of a severely
09:56:45 14 hypertriglyceridemic patient?

09:56:45 15 A Yes, so it's mentioned in the table and in the text below
09:56:49 16 the table. It's also mentioned in the warnings and
09:56:51 17 precautions section of the label.

09:56:54 18 MR. M. KENNEDY: Mr. Brooks, could we go to the
09:56:56 19 bottom of the right-hand column on table -- sorry, bottom of
09:57:02 20 the right-hand column on table -- sorry, that's right. I
09:57:08 21 apologize, this is the correct place.

09:57:08 22 BY MR. M. KENNEDY:

09:57:10 23 Q So, Dr. Budoff, is this the area of the Lovaza label you
09:57:13 24 were just referring to?

09:57:15 25 A Yes.

09:57:15 1 Q In particular, the discussion at the bottom that begins
09:57:19 2 "in some patients," is that the warning you were referring to?

09:57:23 3 A Yes. So literally here it says,
09:57:31 4 "Lovaza increased low-density lipoprotein...
09:57:35 5 levels in some patients. LDL levels should be
09:57:39 6 monitored periodically during Lovaza therapy."

09:57:42 7 Q Now, could you characterize how often you prescribe
09:57:47 8 Lovaza to your STG patients earlier in your career compared to
09:57:47 9 now.

09:57:50 10 A Yeah, so before Vascepa became available, I used this a
09:57:54 11 fair amount. The -- it was increasingly being used.

09:57:58 12 Again, there was a competition between should I use
09:58:01 13 a fibrate or should I use Lovaza. They both had robust
09:58:06 14 reductions in triglycerides, 50 percent. They both had that
09:58:10 15 adverse or negative side effect of raising LDL cholesterol.

09:58:14 16 So depending on the patient and their coverage, I
09:58:17 17 would use one of these two therapies quite frequently.

09:58:21 18 Q So when you did use Lovaza, for how long would you
09:58:24 19 prescribe it?

09:58:25 20 A So, again, it was always prescribed -- I always
09:58:27 21 prescribed things as a one year initial prescription because
09:58:31 22 that's the longest I can legally prescribe it, but my intent
09:58:34 23 was always, once I deemed that they needed the Lovaza, it was
09:58:37 24 for lifetime treatment.

09:58:38 25 Q Now, in the period before Vascepa was available, were

09:58:43 1 clinicians concerned about the LDL-C effects of fibrates and
09:58:47 2 Lovaza?

09:58:47 3 A Yes.

09:58:48 4 Q Did clinicians nonetheless prescribe fibrates and Lovaza?

09:58:53 5 A Yes. They were the only drugs available, basically,
09:58:57 6 widely available. There is niacin as well, but niacin came
09:59:01 7 with a lot of flushing, and that would usually limit its use.

09:59:05 8 So I would say a vast majority of clinicians -- we
09:59:09 9 had to get the triglycerides out of the severe range. Diet
09:59:12 10 and exercise already failed by definition before we would
09:59:16 11 start a therapy, so now these patients have a genetic cause, a
09:59:20 12 lifetime problem, and need to be treated long-term with either
09:59:23 13 Lovaza or fibrate therapy.

09:59:26 14 MR. M. KENNEDY: Sir, I would like to turn to
09:59:28 15 Vascepa now. And, Mr. Brooks, could I have PX 1186 which has
09:59:33 16 already been admitted into evidence.

09:59:33 17 BY MR. M. KENNEDY:

09:59:37 18 Q And, Dr. Budoff, do you recognize this document?

09:59:39 19 A Yes.

09:59:39 20 Q What is it?

09:59:40 21 A This is the prescribing information or label for Vascepa
09:59:45 22 as of December 2019.

09:59:48 23 Q Is this a document you relied on in forming your opinions
09:59:51 24 in this case?

09:59:52 25 A Yes.

09:59:53 1 Q So I would like to turn to page 11 of this document,
09:59:57 2 which should be table 2. I think we looked at this yesterday.

10:00:02 3 But, Dr. Budoff, do you have an understanding of
10:00:06 4 where the data in table 2 of the Vascepa label came from?

10:00:10 5 A Yes, the MARINE study.

10:00:12 6 Q So before we go on, were you in the courtroom yesterday
10:00:14 7 when Dr. Ketchum testified?

10:00:16 8 A Yes.

10:00:16 9 Q So I would like to turn to a question that the Court
10:00:19 10 asked and have you address it, and I believe the question was
10:00:24 11 how do you know that the effects shown in table 2 are
10:00:27 12 attributable to Vascepa and not to diet and lifestyle
10:00:31 13 improvement.

10:00:32 14 Do you remember that question from yesterday
10:00:34 15 morning?

10:00:35 16 A Yes.

10:00:35 17 Q So are the effects shown in table 2 attributable to
10:00:39 18 Vascepa and not diet and lifestyle?

10:00:42 19 A Yes. So the way that the MARINE trial was done is
10:00:45 20 concordant with how the prescribing information is written
10:00:49 21 that first you try and you implement diet and lifestyle, and
10:00:54 22 in the MARINE trial that's how it was done.

10:00:57 23 For six to nine weeks before they started -- got
10:01:07 24 randomized, they were put on diet and lifestyle treatment, so
10:01:07 25 the effect of diet and lifestyle already came into play.

10:01:09 1 Then we measured their baseline variables, and you
10:01:13 2 can see the word baseline here. That's after the effect of
10:01:17 3 diet and lifestyle.

10:01:18 4 So the first way we know this is not due solely to
10:01:21 5 diet and lifestyle is that that has already been implemented
10:01:25 6 and continued throughout the trial.

10:01:27 7 So these baseline variables are then, if they still
10:01:30 8 had severe hypertriglyceridemia -- so it's very important to
10:01:33 9 understand because we've eliminated all of those patients, as
10:01:38 10 we are supposed to before prescribing Vascepa, we've
10:01:42 11 eliminated all of those patients where diet and lifestyle
10:01:46 12 fixed the problem.

10:01:47 13 In other words, I put them on diet and lifestyle if
10:01:50 14 I was investigator in MARINE, their triglycerides dropped to
10:01:54 15 450, they're no longer able to get randomized in the trial
10:01:59 16 because they do not have severe hypertriglyceridemia at the
10:02:02 17 time of the randomization.

10:02:05 18 So the other way we know that this is not due to
10:02:08 19 diet and lifestyle is that both the Vascepa group and the
10:02:11 20 placebo group both are getting diet and lifestyle throughout
10:02:16 21 the trial. So the effect on diet and lifestyle would be
10:02:20 22 neutral because it's -- it's reflected in both groups.

10:02:24 23 And the only difference between group A, Vascepa,
10:02:28 24 and group B, placebo, is the drug itself. So the effects are
10:02:32 25 only from the drug and not due to the diet and lifestyle

influence.

Q So at a high level, how does the data in table 2 for Vascepa compare to the data we just looked at for Lovaza?

A Yeah, so, again, the primary reason, the indication for Vascepa is to lower triglycerides in the setting of severe hypertriglyceridemia.

So we look at the triglyceride results at the top, and at the far right you can see the difference. The net effect is minus 33 percent, so not quite as robust as Lovaza, not quite as robust as fibrates, but it does nicely reduce triglycerides by about a third.

If we look at the placebo group, and look at the percent change, it's plus ten percent. Just like we saw with the Lovaza group, Lovaza was plus seven percent, that the net effect of continuing diet and exercise once you've employed it, does not generally reduce triglycerides in most patients.

The average increase was -- there was an actual average increase over time if they were just maintained on diet and exercise. Remember, placebo is placebo plus diet and exercise. Vascepa, is Vascepa plus diet and exercise.

Q So moving to the LDL-C row, how does the LDL-C data shown here compare to the data we saw with Lovaza?

A Yeah, so the LDL-C -- and this is dramatically different than both fibrates and Lovaza. Now, instead of plus 49 percent, it's minus two percent.

1 The net effect of putting somebody on Vascepa is
2 that LDL-C does not go up. So this is much different with
3 much different cardiovascular implications for a patient
4 because their LDL is not going up by 50 percent.

5 Q So how did this clinical data affect your treatment
6 decisions for your patients with severe hypertriglyceridemia?

7 A So now this became the preferred agent when it was
8 available.

9 Remember, there are still formulary issues. There
10 are still cost issues because this is not generic, and Lovaza
11 had a generic alternative at this time. But this would be a
12 very compelling reason for clinicians to use Vascepa.

13 And I would argue in the setting of severe
14 hypertriglyceridemia, the only reason to use it, because it's
15 not as good a triglyceride lowering agent as Lovaza, so the
16 reason you would pick a branded drug over Lovaza is going to
17 be almost solely due to the LDL-C drop.

18 Q But how do you know what other clinicians are doing in
19 response to the Vascepa data?

20 A Well, I spend quite a bit of time lecturing. Literally
21 this afternoon I was supposed to be lecturing to the family
22 medicine doctors at my institution on hypertriglyceridemia and
23 hyperlipoidemia. I had to move that lecture.

24 But I literally interact with primary care doctors
25 on a daily basis. I educate them on this, and I know what

10:05:54 1 they're doing in practice, and try to direct them to guideline
10:05:59 2 evidence-based medicine of what the best practices are at this
10:06:03 3 point in time because obviously that continues to change over
10:06:06 4 time.

10:06:06 5 Q When you do prescribe Vascepa to your STG patients, for
10:06:11 6 how long do you typically prescribe it?

10:06:13 7 A So, again, once I've already eliminated the short-term
10:06:17 8 causes, I've made sure they're not a diabetes person out of
10:06:20 9 control, I make sure that their thyroid disease is controlled,
10:06:23 10 I've put them on good lifestyle and diet, and all of that has
10:06:28 11 failed, as per the label, I then institute Vascepa, and I
10:06:32 12 institute Vascepa for life, because the only people left are
10:06:35 13 people with genetic abnormalities that cause permanent
10:06:40 14 elevations in their triglycerides. So it's always a lifetime
10:06:44 15 treatment.

10:06:45 16 Q Sir, are you familiar with the proposed labels that will
10:06:49 17 accompany defendants' ANDAs in this case?

10:06:51 18 A Yes.

10:06:52 19 MR. M. KENNEDY: Mr. Brooks, could we please
10:06:53 20 have Plaintiffs' Exhibit 1203 which I believe has been
10:06:57 21 pre-admitted in this case.

10:06:57 22 BY MR. M. KENNEDY:

10:07:03 23 Q Dr. Budoff, do you recognize this document?

10:07:05 24 A Yes.

10:07:06 25 Q What is it?

10:07:06 1 A So this is the package insert or label for the generic
10:07:13 2 proposed alternative to Vascepa. I believe this is the Hikma
10:07:17 3 version.

10:07:19 4 MR. M. KENNEDY: Okay. Could we pull up
10:07:22 5 Plaintiffs' Exhibit 1209 -- I'm sorry.

10:07:22 6 BY MR. M. KENNEDY:

10:07:25 7 Q Dr. Budoff, did you rely on Plaintiffs' Exhibit 1203 in
10:07:29 8 forming your opinions in this case?

10:07:30 9 A Yes.

10:07:30 10 Q Okay. So let me ask you about Plaintiffs' Exhibit 1209.
10:07:34 11 Do you recognize this document?

10:07:36 12 A Yes.

10:07:36 13 Q What is it?

10:07:37 14 A So this is the label, or proposed label, for the generic
10:07:45 15 alternative to Vascepa. I believe this is the Dr. Reddy's
10:07:48 16 Labs' version.

10:07:50 17 Q Is this a document you relied on in forming your opinions
10:07:53 18 in this case?

10:07:54 19 A Yes.

10:07:55 20 MR. M. KENNEDY: Your Honor, we would like to
10:07:56 21 admit PX 1209 into evidence.

10:07:58 22 MR KLEIN: No objection.

10:08:00 23 THE COURT: 1209 is admitted.

10:08:00 24 (Plaintiffs' Exhibit 1209 received in
10:08:00 evidence.)
10:08:00 25

10:08:00 1 BY MR. M. KENNEDY:

10:08:05 2 Q Dr. Budoff, how do the proposed labels for Hikma's ANDA
10:08:08 3 product and DRL's ANDA product compare to one another?

10:08:12 4 A They are very, very similar.

10:08:14 5 Q Are there any differences between those two labels that
10:08:18 6 are material to your infringement opinions in this case?

10:08:22 7 A No. The only difference is I think one is proposing a .5
10:08:27 8 gram dose and one is not.

10:08:28 9 Q Is that difference material to any of your opinions you
10:08:31 10 will be giving today?

10:08:32 11 A No.

10:08:33 12 Q How do the Hikma and DRL labels as of today compare to
10:08:38 13 the Vascepa label PX 1186 that we looked at earlier?

10:08:42 14 A It is very, very similar. I think the only material
10:08:46 15 difference is every time the word Vascepa appeared in the
10:08:49 16 Vascepa label, the word icosapent ethyl appeared in the
10:08:54 17 icosapent ethyl in these generic proposed labels.

10:08:58 18 Q Does that word substitution affect any of your
10:09:01 19 infringement opinions in this case?

10:09:03 20 A No.

10:09:03 21 Q Does the Vascepa label as it exists today have the same
10:09:07 22 indications as the DRL and Hikma labels as they exist today?

10:09:13 23 A The indications here are only for severe
10:09:17 24 hypertriglyceridemia. They do not appear to have the
10:09:21 25 REDUCE-IT indications listed in the generics, but my opinions

10:09:26 1 are based on the infringement of severe hypertriglyceridemia
10:09:29 2 so the indications read word for word the same between the
10:09:34 3 three labels.

10:09:34 4 Q So if I asked for your opinions today regarding the
10:09:37 5 Vascepa label, PX 1186, would your opinion be the same if I
10:09:43 6 had asked you about the Hikma label, PX 1203, or the DRL
10:09:48 7 label, PX 1209?

10:09:50 8 A Yes.

10:09:51 9 MR. M. KENNEDY: So, Mr. Brooks, could we go
10:09:53 10 back to PX 1186, the current Vascepa label.

10:09:53 11 BY MR. M. KENNEDY:

10:09:58 12 Q And let me just kind of go through some of the key
10:10:02 13 portions we will be looking at today, starting with the
10:10:04 14 indications and usage section.

10:10:07 15 And, generally, what's the purpose of the
10:10:09 16 indications and usage section?

10:10:11 17 A You know, so this is, I think, you know, a very important
10:10:15 18 part of the label.

10:10:16 19 This is where we decide whether or not my patient
10:10:19 20 fits into the type of patients that are indicated. In other
10:10:24 21 words, does this go along with the approved use of the drug,
10:10:27 22 is my patient indicated to be on this therapy.

10:10:31 23 Q And let's go to the dosage and administration section.

10:10:35 24 At a high level, what's the purpose of the dosage
10:10:38 25 and administration section in the label?

10:10:41 1 A Yeah, so once I've established that the patient is
10:10:44 2 indicated to be on the drug, I then have to read about how to
10:10:47 3 initiate or prescribe the therapy. So this tells me what to
10:10:52 4 do prior to initiation of Vascepa and then how to prescribe
10:10:58 5 Vascepa specifically.

10:11:00 6 MR. M. KENNEDY: Let's go, Mr. Brooks, to the
10:11:02 7 warnings and precautions section which cuts across pages 2 and
10:11:06 8 3.

10:11:06 9 BY MR. M. KENNEDY:

10:11:07 10 Q What do you get as a physician from the warnings and
10:11:10 11 precautions section?

10:11:12 12 A So this is another very important section of the label.
10:11:15 13 This warns me about things I need to be aware of, things I
10:11:19 14 might need to inform my patients about when prescribing this
10:11:23 15 therapy.

10:11:24 16 MR. M. KENNEDY: Mr. Brooks, we already looked
10:11:26 17 at the clinical study section which is 14, so let's go to the
10:11:30 18 patient counseling information, section 17.

10:11:30 19 BY MR. M. KENNEDY:

10:11:36 20 Q And, Dr. Budoff, what is the purpose of the patient
10:11:38 21 counseling and information section?

10:11:40 22 A As you can see here, and this is pages 11 and 12 of this
10:11:44 23 label, that it basically tells us what we should inform our
10:11:49 24 patients when prescribing this therapy.

10:11:52 25 So it gives us a list of things that we should do,

10:11:55 1 things that we should inform our patients about, things that
10:11:58 2 we should advise our patients about when starting Vascepa
10:12:03 3 therapy.

10:12:04 4 Q So when you talk to your STG patients, is the advice that
10:12:08 5 you give them consistent with what's in section 17 of the
10:12:13 6 Vascepa label?

10:12:14 7 A Yes.

10:12:15 8 MR. M. KENNEDY: Mr. Brooks, if we could go to
10:12:17 9 the patient information portion.

10:12:17 10 BY MR. M. KENNEDY:

10:12:23 11 Q Now, Dr. Budoff, what is the purpose of the patient
10:12:26 12 information section?

10:12:28 13 A Yeah, so this is literally a handout that you can give
10:12:32 14 patients. I do sometimes, depending on the patient. But when
10:12:36 15 I prescribe a new therapy, the pharmacist may give this out to
10:12:40 16 the patient when they first give them a new treatment.

10:12:45 17 This is information for the patient. It's written
10:12:48 18 in lay language, and it goes through a lot of the same
10:12:51 19 sections, but it's all lay language on what should the patient
10:12:56 20 do, how should the patient take the medicine, how should the
10:13:00 21 patient store the medicine.

10:13:01 22 So it has slightly different information. It's all
10:13:04 23 based on the patient's -- what the patient needs to know when
10:13:07 24 starting Vascepa.

10:13:07 25 Q Now, we've looked at several sections of the Vascepa

1 label, PX 1186. I think you testified that the generics are
2 not seeking the new Vascepa indication.

3 Aside from that, are there any differences in any of
4 the sections we've just looked at between the Vascepa label on
5 the one hand and the proposed Hikma and DRL labels on the
6 other hand?

7 A There are no material differences that affected my
8 opinion in this case.

9 Q Were you instructed about the legal standard to be used
10 in evaluating whether a patent claim has been infringed?

11 A Yes.

12 Q Have we prepared a slide summarizing your understanding
13 of that standard?

14 A Yes.

15 MR. M. KENNEDY: Mr. Brooks, if we could have PX
16 2-9.

17 BY MR. M. KENNEDY:

18 Q Dr. Budoff, does this slide, PX 2-9, represent the legal
19 standard that you've been given?

20 A Yes.

21 Q And so what is the first step in determining
22 infringement?

23 A So, that a -- what a person of ordinary skill in the art
24 would understand or from the claims at the time of the
25 invention.

10:14:13 1 Q And you understand the Court's already performed step one
10:14:16 2 of this analysis.

10:14:17 3 A Yes.

10:14:17 4 Q And then what's step two of the infringement analysis?

10:14:21 5 A So step two is to compare the claims and then determine
10:14:26 6 whether, if you followed the label, would you infringe on the
10:14:31 7 patent itself.

10:14:32 8 Q And have you been instructed about the legal standard to
10:14:37 9 be used in evaluating whether a defendant is inducing
10:14:40 10 infringement of a patent claim?

10:14:43 11 A Yes.

10:14:44 12 MR. M. KENNEDY: Mr. Brooks, could we please
10:14:45 13 have PDX 2-10.

10:14:45 14 BY MR. M. KENNEDY:

10:14:48 15 Q I'm sorry, one more question about the previous standard.
10:14:50 16 Did you apply the standard for infringement that we just
10:14:54 17 looked at in forming your opinions in this case?

10:14:56 18 A Yes.

10:14:57 19 Q So let's look at PDX 2-10.

10:15:01 20 Could you just give your understanding of induced
10:15:04 21 infringement.

10:15:05 22 A Yes. So, this is -- inducement is when the label
10:15:10 23 encourages or recommends or instructs a clinician to meet the
10:15:18 24 limitations or elements, each of the elements in the claim.

10:15:21 25 Q And from what point of view are the labels interpreted?

10:15:25 1 A So the labels are interpreted from a practicing clinician
10:15:30 2 in the field or a person of ordinary skill in the art.

10:15:32 3 Q And which portions of the label do you look at in this
10:15:36 4 analysis?

10:15:37 5 A So the label is taken in its entirety.

10:15:40 6 Q I would like to move on to the infringement issues in
10:15:43 7 this case. Are you familiar with the patents-in-suit?

10:15:46 8 A Yes.

10:15:47 9 Q Oh, sorry one more question about PDX 2-10.

10:15:52 10 What is your understanding of .2 here under the
10:15:56 11 induced infringement standard?

10:15:58 12 A That it would be at least some clinicians would
10:16:05 13 inevitably infringe on the label if they -- if they -- if they
10:16:11 14 followed the methods or if they were encouraged by the label
10:16:16 15 to meet all of the elements.

10:16:17 16 Q Okay. Now let's move on to the patents-in-suit in this
10:16:21 17 case, and I would like to start with PDX 21, which is on the
10:16:26 18 list of pre-admitted exhibits.

10:16:29 19 Dr. Budoff, do you recognize this document?

10:16:32 20 A Yes.

10:16:32 21 Q What is it?

10:16:33 22 A This is patent '728.

10:16:36 23 Q And the full number being patent 8293728?

10:16:41 24 A Yes.

10:16:42 25 Q Is this a patent you relied on in forming your opinions

10:16:46 1 in this case?

10:16:46 2 A Yes.

10:16:46 3 Q Now, again, in performing your infringement analysis,
10:16:52 4 were there any relevant differences between the Vascepa label
10:16:55 5 and either of the defendants' label?

10:16:57 6 A No.

10:16:58 7 Q So that being the case, if I asked you about the Vascepa
10:17:01 8 label, would you have the same opinion if I had asked you
10:17:03 9 about the Hikma or DRL labels?

10:17:06 10 A Yes.

10:17:06 11 Q So have you prepared a slide reproducing each element of
10:17:10 12 claim 1 of the '728 patent?

10:17:13 13 A Yes.

10:17:13 14 MR. M. KENNEDY: So, Mr. Brooks, can we have
10:17:16 15 PDX 2-11.

10:17:16 16 BY MR. M. KENNEDY:

10:17:19 17 Q Is this the slide I just referred to?

10:17:21 18 A Yes.

10:17:21 19 Q And there is a notation here that says stipulated. What
10:17:25 20 does that mean?

10:17:26 21 A So my understanding is that the -- both sides have
10:17:30 22 already agreed that this claim element would be met by the --
10:17:34 23 by the labels.

10:17:37 24 MR. M. KENNEDY: So, Your Honor, let me just
10:17:38 25 note for the record the stipulated facts associated with this

particular stipulation are paragraphs 204 to 209 for Amarin's Vascepa product and label, 216 to 221 for Hikma's product and proposed label, and 228 to 234 for DRL's proposed label.

THE COURT: Thank you.

BY MR. M. KENNEDY:

Q So, Dr. Budoff, reviewing the claim elements for claim 1 of the '728 patent, do you follow the steps here when you use or when you administer Vascepa to treat patients with severe hypertriglyceridemia?

A Yes.

Q In your view, would other clinicians do the same thing?

A Yes.

Q Would somebody following the labeling of the Vascepa product follow every element of claim 1 of the '728 patent?

A Yes. The label encourages these steps to be taken and all of these elements to be met when prescribing these therapies.

Q So let's take these elements one at a time.

Have you formed an opinion concerning whether the contents of the Vascepa label encourages clinicians to prescribe Vascepa to a subject having a baseline triglyceride -- a fasting baseline triglyceride level of 500 milligrams per deciliter to about 1500 milligrams per deciliter as required by claim 1 of the '728 patent?

A Yes.

10:19:03 1 Q What is that opinion?

10:19:05 2 A So the indication for these therapies is for severe
10:19:10 3 hypertriglyceridemia, to lower triglycerides, so literally
10:19:13 4 this is the indication, the literal indication of the drug to
10:19:16 5 reduce severe -- to reduce triglycerides in a subject with
10:19:21 6 severe hypertriglyceridemia, and that's greater or equal to
10:19:26 7 500 milligrams per deciliter.

10:19:27 8 MR. M. KENNEDY: Mr. Brooks, could we have PX
10:19:30 9 1186, the indications and usage section, and I would like to
10:19:35 10 look at the second bullet point.

10:19:35 11 BY MR. M. KENNEDY:

10:19:37 12 Q Dr. Budoff, is this the indication you just referred to?

10:19:41 13 A Yes. Yesterday, I think they called this the MARINE
10:19:45 14 indication, and this is the literally almost word for word of
10:19:48 15 that first element.

10:19:49 16 Q And does each defendants' proposed label have the same
10:19:52 17 indication?

10:19:53 18 A Yes.

10:19:53 19 MR. M. KENNEDY: Could we go to the clinical
10:19:55 20 study section, table 2.

10:19:55 21 BY MR. M. KENNEDY:

10:20:00 22 Q Is there anything in the clinical study section relevant
10:20:03 23 to your opinion that the first element of claim 1 of the '728
10:20:08 24 patent is met?

10:20:09 25 A Yes. I mean, this, again, is in patients with severe

hypertriglyceridemia, and it demonstrates that use of the drug will reduce triglycerides here by an average of 33 percent.

Q Do you understand that the other asserted claims in this case have the same or very similar claim language to the element we just looked at concerning the 500 to 1500 milligrams per deciliter patient?

A Yes.

MR. M. KENNEDY: Mr. Brooks, could we have PX 2-12.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, what does this slide depict?

A So this basically just shows two slightly different claim languages and which claims use those specific claim languages.

Q And the opinion you just expressed with respect to the version of this element that appears in claim 1 of the '728 patent, would those opinions apply with equal force with the same or similar claim language that appears in the other asserted claims?

A Yes.

Q So let's move on to PDX 2-13, and this is the claim limitation requiring administration of the drug for a period of 12 weeks.

Have you formed any opinions concerning whether the contents of the Vascepa label encourage clinicians to prescribe Vascepa to their severely hypertriglyceridemic

10:21:35 1 patients for a period of 12 weeks as required by claim 1 of
10:21:39 2 the '728 patent?

10:21:42 3 A Yes.

10:21:42 4 Q What is that opinion?

10:21:43 5 A That physicians, the average clinician practicing in the
10:21:49 6 field will prescribe Vascepa for long-term therapy which will
10:21:55 7 encompass a period of 12 weeks.

10:21:57 8 Q And would you have the same opinion if I'd ask you about
10:22:00 9 the Hikma label, PX 1203, or the DRL label, PX 1209?

10:22:06 10 A Yes.

10:22:07 11 Q So let's go to the indications and usage section of the
10:22:10 12 Vascepa label.

10:22:12 13 And, again, I would like to look at what we're
10:22:15 14 calling the MARINE indication, which reads,

10:22:17 15 "As an adjunct to diet to reduce TG levels in
10:22:21 16 adult patients with severe, over 500 milligrams per
10:22:25 17 deciliter, hypertriglyceridemia."

10:22:28 18 Does the indications and usage by itself tell
10:22:31 19 you anything or tell a clinician anything about the duration
10:22:35 20 for which you should prescribe Vascepa?

10:22:38 21 A Yes.

10:22:39 22 Q What does it tell you?

10:22:40 23 A Well, clinicians in the field will know that severe
10:22:45 24 hypertriglyceridemia is largely a genetic problem, a lifelong
10:22:50 25 problem, and requires lifelong therapy. So when the

1 indication lists a chronic disease, then the treatment is
2 long-term.

3 Q Is there anything in the indications and usage of the
4 Vascepa label that tells you a maximum length of time for
5 prescribing Vascepa?

6 A No, there's no limit put here as there would be if this
7 was a short-term treatment for an acute condition.

8 Q Are the words adjunct to diet relevant to the length of
9 time for which a clinician should prescribe Vascepa according
10 to the label?

11 A Yes, and it's brought out again in the dosage and
12 administration section talking about lifestyle and nutritional
13 intake and physical activity, that it's maintaining this --
14 maintaining this therapy over the long run because you've
15 already eliminated the short-term problems of a bad life style
16 or a bad diet or too much alcohol use.

17 So after diet, you then -- and they still have high
18 triglycerides, then Vascepa is indicated. So you've
19 eliminated short-term and now you're left with only the
20 chronic genetic patients.

21 Q So let's go to the dosage and administration section
22 which is immediately below. I would like to ask you about
23 section 2.1 prior to initiation of Vascepa. What does it mean
24 to initiate Vascepa?

25 A So prior to starting or prescribing Vascepa, they give

10:24:27 1 you some steps that you should take and accomplish prior to
10:24:32 2 implementing treatment.

10:24:33 3 Q Let me just back up just for a second. What does the
10:24:37 4 word initiation mean in this context?

10:24:39 5 A Oh, to start the therapy or to prescribe the therapy.

10:24:42 6 Q So let's talk about the first bullet point under the
10:24:46 7 words "Prior to Initiation of Vascepa." What is this first
10:24:52 8 bullet point of the label telling you to do?

10:24:54 9 A So it specifically tells you to identify other causes,
10:24:59 10 and we talked about the short-term or the secondary causes
10:25:03 11 that can cause transient elevations in triglycerides, such as
10:25:09 12 poorly controlled diabetes or low thyroid disease, and manage
10:25:13 13 those as appropriate first.

10:25:15 14 And if there's still a problem where the
10:25:17 15 triglycerides are still above 500 and they still have severe
10:25:21 16 hypertriglyceridemia, then you can go on to the next step.

10:25:24 17 Q So you mentioned transient causes. Is that the same
10:25:27 18 thing as -- I think you mentioned reversible causes earlier?

10:25:30 19 A Yes.

10:25:31 20 Q So let's say you follow the first bullet point under 2.1,
10:25:37 21 you identify these other reversible causes such as diabetes,
10:25:47 22 hyperthyroidism, and medications, and you manage them as
10:25:48 23 appropriate, and let's say you successfully manage them. At
10:25:51 24 that point would those patients get Vascepa?

10:25:54 25 A No. Just like the MARINE trial, if they don't still have

1 severe hypertriglyceridemia, they would never be implemented
2 on treatment.

3 Q And then let's go the second bullet point under
4 section 2.1 which reads, quote,

5 "Patients should engage in appropriate
6 nutritional intake and physical activity before
7 receiving Vascepa which should continue during
8 treatment with Vascepa."

9 So what -- you've probably touched on this
10 earlier, but what does this involve?

11 A So, again, this is what I talked about earlier. The way
12 the MARINE trial was literally done, you first counsel them
13 and get them to engage in a good diet and exercise.

14 If good diet and exercise fail, then you would
15 initiate Vascepa. If good diet and exercise is successful,
16 you don't use Vascepa. It would be off-label use to use
17 Vascepa before implementing diet and exercise.

18 Q So if it's one of those patients who you can counsel them
19 on diet and lifestyle, and that gets them under 500 and keeps
20 them there, would that patient get prescribed Vascepa if the
21 clinician were following the label?

22 A No.

23 Q So would -- so if you back out the patients who have what
24 you are calling reversible causes, and you're backing out the
25 patients who have diet and lifestyle related issues that get

10:27:22 1 them over 500, who is left?

10:27:24 2 A So left -- as we saw in that table from the scientific
10:27:30 3 statement from the American Heart Association, the only
10:27:32 4 category that's left is genetic causes.

10:27:35 5 Q And do those people get Vascepa if a clinician is
10:27:39 6 following the labeling, the people with genetic causes?

10:27:42 7 A Yes. They have a lifetime problem, and they're going to
10:27:45 8 develop pancreatitis, their risk of developing pancreatitis is
10:27:50 9 high, so they would get Vascepa as encouraged by the label
10:27:54 10 here in dosage and administration.

10:27:56 11 Q Would a clinician following the label prescribe Vascepa
10:27:56 12 to somebody whose cause of STG was addressed by something
10:28:04 13 mentioned in section 2.1 of the label?

10:28:06 14 A I'm sorry, can you repeat that?

10:28:07 15 Q Would somebody whose STG was adequately addressed by one
10:28:13 16 of the issues mentioned in 2.1 of the label be prescribed
10:28:19 17 Vascepa by a clinician following the label as a whole?

10:28:19 18 A No, they would be eliminated from being a candidate for
10:28:22 19 Vascepa.

10:28:23 20 Q So let's turn to the clinical study section of the
10:28:26 21 Vascepa label. And, Dr. Budoff, does the clinical study --

10:28:35 22 MR. M. KENNEDY: Mr. Brooks, can we have the
10:28:37 23 verbiage above table 2 as well this time? Sorry.

10:28:37 24 BY MR. M. KENNEDY:

10:28:42 25 Q Dr. Budoff, does the clinical study section of the

10:28:45 1 Vascepa label tell you anything about the duration of
10:28:49 2 treatment that the label is calling for, for Vascepa?

10:28:51 3 A Well, yes. I mean, the study designed specifically calls
10:28:56 4 out that patients were enrolled in this study for 12 weeks.

10:28:59 5 Q Why is that meaningful?

10:29:01 6 A Well, because, in clinical practice, we -- we try to
10:29:08 7 follow the prescribing information, and if the prescribing
10:29:12 8 information was done at 12 weeks, then that informs the
10:29:15 9 physician, that instructs the physician that you should wait
10:29:19 10 12 weeks to reassess lipids to see what the full effect of
10:29:23 11 your treatment is, because my goal, when putting them on
10:29:26 12 Vascepa, is to achieve the results in table 2.

10:29:30 13 In other words, I want to see a 33 percent drop on
10:29:34 14 average in triglycerides. I want to see no rise in LDL
10:29:39 15 cholesterol.

10:29:39 16 So those become really important, and the only way I
10:29:42 17 can compare my patient to the label and what's being
10:29:47 18 encouraged is to follow the instructions that are given, and
10:29:51 19 the instructions here are to treat for 12 weeks.

10:29:57 20 Q Does the Vascepa label contain any clinical data
10:30:00 21 concerning treatment of Vascepa for any duration other than
10:30:04 22 12 weeks, like, for example, four weeks?

10:30:05 23 A No, there's no other mention of any other duration of
10:30:09 24 treatment other than 12 weeks.

10:30:10 25 Q So if you, for some reason, decided to prescribe Vascepa

10:30:14 1 for four weeks to a severe hypertriglyceridemic patient, what
10:30:19 2 would the label tell you about what lipid effects you would
10:30:23 3 expect to achieve?

10:30:24 4 A So there are none listed here, so the label would not
10:30:27 5 inform you at all on what to expect at four weeks.

10:30:30 6 Q And, again, just to -- the clinical studies data in
10:30:36 7 table 2 of the Vascepa label, does the same data appear in the
10:30:38 8 DRL and Hikma labels?

10:30:38 9 A Yes, the same exact language for 12 weeks exists.

10:30:42 10 Q The same data as well?

10:30:43 11 A Yes.

10:30:43 12 Q Dr. Budoff, is there any background information a
10:30:47 13 clinician in this field would bring to bear when reading the
10:30:52 14 Vascepa label?

10:30:53 15 A Yes. I mean, physicians who are treating patients with
10:30:56 16 severe hypertriglyceridemia are generally either going to be
10:31:00 17 primary care physicians, largely, may be endocrinology or
10:31:04 18 cardiology, and they will be familiar with other therapies in
10:31:08 19 the class. They're supposed to be familiar with the
10:31:10 20 guidelines, and they are supposed to follow the label when
10:31:14 21 prescribing these therapies.

10:31:15 22 Q So the clinicians who would be reading the Vascepa label,
10:31:19 23 they would already know what severe hypertriglyceridemia is?

10:31:23 24 A Yes, I would hope so. Usually the physician who starts
10:31:27 25 therapy understands the disease well enough to implement

10:31:31 1 treatment for that disease.

10:31:32 2 MR. M. KENNEDY: Mr. Brooks, could we have PX
10:31:34 3 288.

10:31:34 4 BY MR. M. KENNEDY:

10:31:39 5 Q Dr. Budoff, do you recognize this document?

10:31:42 6 A Yes.

10:31:43 7 Q What is it?

10:31:44 8 A So, this is a review article written by Dr. Karalis, he's
10:31:51 9 a professor and cardiologist in Pennsylvania.

10:31:56 10 Q Generally what's the subject matter of this article?

10:31:59 11 A So this is a review of all of the clinical guidelines for
10:32:03 12 how to manage hypertriglyceridemia, and in this paper he
10:32:09 13 focuses more on the treatment with the 4-gram doses of omega-3
10:32:15 14 fatty acids, the high dose treatments that are available.

10:32:18 15 Q And the omega-3 fatty acids, that refers collectively to
10:32:20 16 Vascepa and Lovaza?

10:32:22 17 A Yes.

10:32:22 18 Q Is this a document you relied on in forming your opinions
10:32:25 19 in this case?

10:32:29 20 A Yes.

10:32:29 21 MR. M. KENNEDY: Your Honor, Amarin moves PX 288
10:32:32 22 into evidence.

10:32:33 23 MR KLEIN: No objection.

10:32:34 24 MR. M. KENNEDY: Or seek to move 288 --

10:32:34 25 THE COURT: 288 is admitted.

(Plaintiffs' Exhibit 288 received in evidence.)

MR. M. KENNEDY: Mr. Brooks, could we go to page 309 of this article, the right-hand column, the section that starts "Patients with very high TG levels."

BY MR. M. KENNEDY:

Q And in particular, Dr. Budoff, I would like to ask you about the sentence that begins "If an individual with very high TG."

Dr. Budoff, what is this sentence telling you about what to do with somebody who falls into one of the very high TG groups?

A Yes, so this describes what we call step-wise care. So, and that's how every physician that I'm familiar with practices.

In other words, you do step one. In this case, let's say we put them on Vascepa therapy. That's step one. Then you see what happens after step one, and you decide if you're going to go to step two.

So this is describing the considerations of going to step two, "consideration should be given to adding a statin to their triglyceride-lowering therapy."

So it's not saying stop step one and start over, it's saying you've already put them on Vascepa, should I add a statin to further reduce their cardiovascular risk.

Q So this passage is talking about somebody who had very

1 high TGs, was put on an omega-3 fatty acid, and now they fall
2 into a lower category of TG level?

3 A So now they're at lower level of TG level, but now
4 they're at an enhanced level of cardiac risk so now my focus
5 shifts.

6 I've treated -- I've successfully treated their high
7 triglycerides. I maintain that, I continue that as outlined
8 here, I continue the Vascepa, and now I say, oh, I've gotten
9 you out of the risk of pancreatitis, but now you're at risk of
10 a heart attack, I better do something else.

11 In this recommendation the something else, based on
12 the 2013 cholesterol guidelines, is to add a statin to their
13 regimen.

14 Q And just to be clear, Dr. Budoff, we're still talking
15 about a patient with severe hypertriglyceridemia?

16 A Yes, the paragraph starts with "patients with very high
17 triglyceride levels."

18 Q So --

19 A So that's literally the population that they're
20 describing in this article.

21 Q And I --

22 THE COURT: Mr. Kennedy, may I interrupt for a
23 moment?

24 MR. M. KENNEDY: Sure.

25 THE COURT: Earlier, Dr. Budoff, there was a

10:35:08 1 chart shown showing a patient with TG equal to or above 500 mg
10:35:16 2 per deciliter, and then you -- I think the chart says the goal
10:35:20 3 was to reduce their TG, and then the next category is between
10:35:24 4 two something, 200 to 499.

10:35:28 5 THE WITNESS: Yes.

10:35:28 6 THE COURT: There's cardiovascular risk. Are
10:35:31 7 you referring to that category of patient?

10:35:35 8 THE WITNESS: Yes. So now we've basically
10:35:37 9 lowered their pancreatitis risk so now we now assess their
10:35:41 10 cardiovascular risk.

10:35:43 11 THE COURT: Thank you.

10:35:43 12 BY MR. M. KENNEDY:

10:35:44 13 Q And, Dr. Budoff, I would like to turn to the last passage
10:35:47 14 in this section here that starts, "If the TG levels fall to a
10:35:52 15 normal or borderline level," and what is this passage saying
10:35:56 16 about how to treat patients who started with severe
10:36:03 17 hypertriglyceridemia?

10:36:04 18 A Yeah, so this is now the scenario that the patient who
10:36:07 19 had very high triglyceride, above 500, severe
10:36:12 20 hypertriglyceridemia, we've implemented lifestyle changes,
10:36:15 21 we've implemented Vascepa or another drug and a statin, and
10:36:18 22 they say if their triglycerides fall to normal or borderline,
10:36:23 23 consideration can be given to discontinue the nonstatin,
10:36:28 24 triglyceride-lowering medication.

10:36:29 25 Q And what is normal or borderline?

1 A So that would be less than -- so normal is less than 150,
2 borderline is less than 200.

3 So implementation in this scenario, when using
4 Vascepa, as an example, if you started above 500, so let's say
5 they're about 600, which is even less than the average in the
6 MARINE trial, to get to 600 to less than 200 would be a 66 --
7 a two-thirds reduction in their -- in their triglyceride
8 levels which would be double what we saw in the trials.

9 So I think this is an unlikely scenario. But if you
10 do happen to achieve reversal of their triglycerides, and they
11 come down to completely normal, then it says consideration can
12 be given to stopping the triglyceride-lowering medication.

13 Q Now, in your own practice how often do you see that kind
14 of magnitude of a reduction from someone who is at very high
15 triglycerides to normal or borderline?

16 A Yes, I could say that -- I can say that I've never seen
17 that in my practice.

18 In the EVAPORATE trial, which was a prospective
19 randomized trial using Vascepa, no patients had a 66 percent
20 drop in their triglycerides using Vascepa therapy.

21 Q Now, if you have a patient with very high triglycerides
22 who achieves a triglyceride reduction with Vascepa short of
23 that kind of 60 -- you know, 70 percent reduction, do you
24 consider taking them off of Vascepa at that point?

25 A No. So if their triglyceride levels are still in the

10:38:08 1 high range, then I know if I stop Vascepa their triglycerides
10:38:12 2 will go back up to baseline.

10:38:15 3 Remember, we've eliminated all of the short-term,
10:38:18 4 all of the bad diets, all of the alcohol bingers, all of the
10:38:21 5 diabetics out of control. What we're left with are the
10:38:25 6 genetic patients, and if I stop the active treatment,
10:38:29 7 triglycerides are going to go back up to where they started,
10:38:31 8 and they're going to be back at risk of pancreatitis.

10:38:35 9 Q So the patients who we're talking about still have --
10:38:38 10 patients we're talking about who have very high triglycerides,
10:38:41 11 and you're able to lower their triglycerides with
10:38:48 12 lipid-lowering therapy, those patients are considered to have
10:38:51 13 the condition of severe hypertriglyceridemia, correct?

10:38:54 14 A Yes, a chronic condition -- you don't take away the
10:38:57 15 diagnosis once you've controlled it. If somebody has high
10:39:01 16 blood pressure, and I treat them, and now their blood pressure
10:39:05 17 is reading normal, I don't tell the patient, oh, you no longer
10:39:08 18 have high blood pressure, the patient has high blood pressure
10:39:09 19 still, they just are treated or have successfully controlled
10:39:13 20 high blood pressure.

10:39:15 21 I just want to point out the last sentence of this
10:39:15 22 paragraph, it says,

10:39:18 23 "Triglyceride levels will need to be
10:39:18 24 monitored closely for any rise in triglycerides."

10:39:21 25 So even Dr. Karalis in their review of the

1 guidelines are reminding you that if you stop the therapy, you
2 best keep an eye on them because they're likely to go back up.

3 Q Would you -- if you put some patient with STG on Vascepa,
4 have you ever seen them have their triglycerides lowered
5 before 500 in less than 12 weeks?

6 A No. I don't measure less than 12 weeks. That's not only
7 a practice with Vascepa, that's a general practice with all
8 lipid-lowering therapies.

9 The statins, for example, the most common practice,
10 the advocated practice, the way the trials were done, is to
11 put them on a new therapy. Let's say I put them on Lipitor, a
12 statin, I would follow them up at three months.

13 I don't get a lipid level at four weeks or
14 six weeks, so I would not know what happens in the short run,
15 I want to see what happens in the long run because this is a
16 chronic disease that's going to be needed to treat long-term.

17 MR. M. KENNEDY: Mr. Brooks, can we go back to
18 PX 989 which we put into evidence earlier today.

19 BY MR. M. KENNEDY:

20 Q And, Dr. Budoff, this is the ATP III we discussed
21 earlier.

22 A Yes.

23 MR. M. KENNEDY: Mr. Brooks, could you please go
24 to page 195, and there's a passage concerning very high
25 triglycerides.

10:40:46 1 BY MR. M. KENNEDY:

10:40:49 2 Q And, Dr. Budoff, what is this passage attempting to
10:40:54 3 convey?

10:40:54 4 A So, again, this goes through -- basically these are the
10:40:59 5 guidelines, but they basically go through the same steps as
10:41:03 6 the label.

10:41:04 7 You start with looking for drugs that could increase
10:41:08 8 triglycerides and preferentially discontinue those drugs. You
10:41:13 9 eliminate alcohol. You make sure that their diabetes is under
10:41:18 10 good control.

10:41:19 11 And then it starts talking about diet and lifestyle
10:41:23 12 changes, and then ultimately what triglyceride-lowering
10:41:26 13 therapies you could institute if all of those first steps are
10:41:30 14 not successful.

10:41:32 15 Q I would like to ask you about towards the end of this
10:41:34 16 passage where it says,

10:41:36 17 "For most persons with extremely high
10:41:38 18 triglycerides, therapy can be considered successful
10:41:41 19 if it reduces serum triglycerides below 500."

10:41:46 20 Do you see that?

10:41:46 21 A Yes.

10:41:46 22 Q What does it mean -- what does the ATP III mean by
10:41:50 23 successful in this context?

10:41:52 24 A Yeah, so all chronic diseases have goals. We always have
10:41:55 25 a goal when we're implementing therapy. Our blood pressure

1 goal is to get the blood pressure down to below 130 or even
2 down to below 120 millimeters of mercury. Our diabetes goals
3 are to achieve a hemoglobin A1C of 6.5.

4 When we achieve those goals, we're considered to be
5 successful. That doesn't mean that we stop therapy, that just
6 means we've achieved our goal, and now we continue therapy, we
7 maintain therapy, to keep the patient at that goal.

8 This is saying the same thing about severe
9 hypertriglyceridemia, that when you get the triglycerides
10 below 500, you've achieved your goal, you've lowered their
11 pancreatitis risk.

12 It says they're often not possible to normalize
13 triglycerides. Going back to what Dr. Karalis talked about,
14 you can -- most of the time you're not getting them down to
15 150 and can stop therapy, you're just getting them under 500,
16 and now you maintain that drug to maintain your goal, so you
17 maintain success over time.

18 Q And in this -- just to clarify, in this context extremely
19 high triglyceride, that means severe hypertriglyceridemia?

20 A Yes.

21 Q And, again, just to clarify, somebody with severe
22 hypertriglyceridemia who is on medication and gets below 500,
23 those patients are still considered to have the condition
24 severe hypertriglyceridemia?

25 A Yes, they have the disease, they're just being

1 controlled. They're controlled for -- with severe
2 hypertriglyceridemia.

3 MR KLEIN: Objection real quickly. I've given
4 counsel a lot of latitude, but there's a fair amount of
5 leading going on.

6 THE COURT: I consider the last few questions
7 summarizing what Dr. Budoff already testified, so to the
8 extent there's an objection, that objection is overruled.

9 BY MR. M. KENNEDY:

10 Q Has FDA expressed a view on whether triglyceride-lowering
11 medication is needed after the patient's TG levels are reduced
12 below 500?

13 A I'm sorry, can you we repeat that?

14 Q I'm sorry. Has FDA expressed a view as to whether
15 TG-lowering medication is needed after a severely
16 hypertriglyceridemic patient is reduced below 500 milligrams
17 per deciliter?

18 A Yes.

19 MR. M. KENNEDY: Let's look at PX 289 which I
20 think is on the list of pre-admitted exhibits.

21 BY MR. M. KENNEDY:

22 Q Dr. Budoff, do you recognize this document?

23 A Yes.

24 Q What is it?

25 A So this was very nicely described by Dr. Ketchum

1 yesterday. This is the medical review, what the FDA publishes
2 to go along with their decision with the -- with the product
3 for, in this case, Vascepa.

4 Q And I would like to go to page 40 of this document.
5 There's a heading called Efficacy Summary.

6 And, Dr. Budoff, does this passage have any
7 significance to your opinion concerning the duration of
8 treatment indicated by the Vascepa label?

9 A Yes. They talk about the indication, and then the second
10 sentence is,

11 "Patients with very high triglycerides have a
12 strong genetic component to their disease and have an
13 increased risk for acute pancreatitis."

14 So, again, genetic implies lifelong problem,
15 implies lifelong treatment.

16 Q Does FDA speak elsewhere in this document to the need to
17 maintain TG-lowering therapy in patients with SHT?

18 A Yes.

19 MR. M. KENNEDY: Mr. Brooks, could we go to
20 page 67.

21 BY MR. M. KENNEDY:

22 Q And directing your attention to the heading 6.1.9, does
23 this passage from the FDA review bear on your opinion
24 concerning the duration of treatment for SHT patients
25 indicated by the Vascepa label?

10:45:48 1 A Yes.

10:45:48 2 Q How so?

10:45:49 3 A So, I mean, this talks about the four-week and the
10:45:51 4 additional 40 weeks, the one year data that was available as
10:45:55 5 described by Dr. Ketchum yesterday, and they just say that the
10:46:00 6 effect of Vascepa 4 grams occurred by week four and the
10:46:04 7 effects were maintained throughout the study.

10:46:06 8 And then the label only talks about the 12-week data
10:46:10 9 because that's the primary target of the trial and our most
10:46:15 10 common practice when we follow-up patients.

10:46:22 11 Q I think you've mentioned this earlier in your testimony,
10:46:24 12 but do you prescribe other lipid-lowering medications other
10:46:28 13 than TG-lowering agents?

10:46:30 14 A Yes.

10:46:31 15 Q Could you give some examples.

10:46:34 16 A In what context?

10:46:35 17 Q Like other than -- you know, anything you prescribe to
10:46:38 18 your patients other than Vascepa, fibrates, or Lovaza.

10:46:41 19 A Yeah, now we use statins, blood pressure medications,
10:46:45 20 many therapies.

10:46:46 21 Q Do some of those other therapies call for indefinite
10:46:51 22 treatment?

10:46:52 23 A Yes. I mean, the label never says treat indefinitely,
10:46:56 24 but the label talks about a chronic condition, and the chronic
10:47:01 25 condition therefore is treated long-term.

10:47:03 1 I think I spoke earlier to when I start a statin,
10:47:08 2 I -- the intent when I put a patient on a statin is that
10:47:12 3 they're going to take it for the rest of their life.

10:47:14 4 MR. M. KENNEDY: Mr. Brooks, could we have PX
10:47:17 5 277.

10:47:17 6 BY MR. M. KENNEDY:

10:47:21 7 Q Dr. Budoff, do you recognize this document?

10:47:23 8 A Yes.

10:47:24 9 Q What is it?

10:47:25 10 A This is the National Lipid Association guidelines
10:47:29 11 published in 2015.

10:47:31 12 Q What is the National Lipid Association?

10:47:34 13 A So the NLA, or the National Lipid Association, is the
10:47:39 14 largest body of physicians who are primarily interested in
10:47:43 15 controlling lipids, so lipids being bad cholesterol, LDL
10:47:48 16 predominantly, and triglycerides, as the two most common that
10:47:52 17 are measured and treated.

10:47:53 18 Q Are these NLA guidelines considered authoritative in your
10:47:58 19 field?

10:47:58 20 A Yes.

10:47:59 21 Q Is this a document you relied on in forming your opinions
10:48:01 22 in this case?

10:48:02 23 A Yes.

10:48:04 24 MR. M. KENNEDY: Your Honor, we would like to
10:48:05 25 enter PX 277.

10:48:07 1 MR KLEIN: No objection.

10:48:09 2 THE COURT: PX 277 is admitted.

10:48:09 3 (Plaintiffs' Exhibit 277 received in
10:48:14 evidence.)

10:48:14 4 MR. M. KENNEDY: And, Mr. Brooks, could we turn
10:48:16 5 to the page marked 154 at the top, and I would like to direct
10:48:21 6 you to the paragraph Follow-Up Visits that cuts across two
10:48:25 7 columns.

10:48:25 8 BY MR. M. KENNEDY:

10:48:28 9 Q Dr. Budoff, does this passage bear on your opinion
10:48:32 10 concerning the duration of treatment indicated by the Vascepa
10:48:35 11 labeling?

10:48:36 12 A Yes. I mean, this -- this starting with the word -- with
10:48:39 13 the very last sentence, once goal levels have been achieved,
10:48:45 14 so this just speaks to you've now achieved your goal or your
10:48:48 15 target, you've been successful as we've described before.

10:48:52 16 "...response to therapy should be
10:48:54 17 monitored...to confirm continued success in
10:48:57 18 maintenance of goal levels and patient adherence."

10:49:02 19 In other words, you don't stop the therapy, you
10:49:04 20 start monitoring them at longer intervals. You don't need to
10:49:08 21 monitor them every three months anymore, but you continue to
10:49:12 22 monitor them over time to make sure that they stay at goal,
10:49:16 23 that you can maintain the success with your therapy, and that
10:49:20 24 they remain -- the patients stay on therapy and they remain
10:49:25 25 adherent.

10:49:25 1 Q Adherent means that the patients are taking the
10:49:28 2 medication as prescribed?

10:49:29 3 A Exactly.

10:49:29 4 Q When you write a prescription, do you intend that
10:49:33 5 patients adhere to that prescription?

10:49:35 6 A Yes, I anticipate that they will follow my instructions,
10:49:38 7 although we all know that not all patients are perfect in
10:49:42 8 following the exact recommendations of their physician.

10:49:45 9 Q Now, are there drugs you encounter in your practice that
10:49:49 10 do have a set limited duration of administration?

10:49:52 11 A Yes.

10:49:52 12 Q Can you think of some examples?

10:49:54 13 A Yes. I mean, the most common example are things like
10:49:58 14 blood thinners like Lovenox or antibiotics. When we prescribe
10:50:04 15 antibiotics, we give a course of antibiotics, we don't give a
10:50:09 16 lifetime of antibiotics.

10:50:11 17 MR. M. KENNEDY: So, Mr. Brooks, could we have
10:50:13 18 PX 285.

10:50:13 19 BY MR. M. KENNEDY:

10:50:18 20 Q And, Dr. Budoff, do you recognize this document?

10:50:20 21 A Yes.

10:50:20 22 Q What is it?

10:50:21 23 A This is the Lovenox package insert or the label for
10:50:26 24 Lovenox.

10:50:27 25 Q And what is Lovenox used for?

10:50:29 1 A So Lovenox is a blood thinner. It's used for acute or
10:50:34 2 short-term conditions surrounding surgery or for acute clots.
10:50:40 3 So we always prescribe a drug that's prescribed for acute or
10:50:44 4 short-term uses for a prescribed length of time.

10:50:48 5 Q Is the Lovenox label a document you relied on in forming
10:50:53 6 your opinions in this case?

10:50:57 7 A Yes.

10:50:57 8 MR. M. KENNEDY: Your Honor, we would like to
10:50:58 9 enter PX 285 into evidence.

10:51:01 10 MR. KLEIN: No objection.

10:51:01 11 THE COURT: 285 is admitted.

10:51:01 12 (Plaintiffs' Exhibit 285 received in
10:51:06 evidence.)

10:51:06 13 MR. M. KENNEDY: Mr. Brooks, could we have
10:51:08 14 section 282 of the Lovenox labeling.

10:51:08 15 BY MR. M. KENNEDY:

10:51:11 16 Q So, Dr. Budoff, is this an example of a drug with a
10:51:16 17 limited duration?

10:51:18 18 A Yes. So this is the dosage section of the label, and it
10:51:24 19 specifically tells you the duration of administration in every
10:51:29 20 single scenario.

10:51:30 21 So it gives you six different indications that
10:51:35 22 Lovenox is indicated for, and in every single circumstance it
10:51:39 23 talks about duration of administration because this is an
10:51:42 24 acute drug that's not used long-term, so you are given this
10:51:48 25 information in the dosage and usage section of the label.

10:51:52 1 Q So I would like to talk to you a little bit about your
10:51:54 2 prescribing practices for Vascepa. Is administering Vascepa
10:51:59 3 for at least 12 weeks consistent with your own practice?

10:52:02 4 A Yes.

10:52:02 5 Q So when you write a new prescription to a patient with
10:52:05 6 severe hypertriglyceridemia for Vascepa, when is the next time
10:52:11 7 you schedule an appointment with them?

10:52:14 8 A Yeah, so the most common practice, the practice that I've
10:52:17 9 been taught, the practice that I teach, is that you follow
10:52:20 10 them up at a three-month interval.

10:52:23 11 You get a lipid value at the end of three months
10:52:25 12 which is, again, approximately 12 weeks, and then you see them
10:52:29 13 a few days after their blood draw so you can review with the
10:52:32 14 patient what the effect of that therapy was over the first
10:52:39 15 12 weeks of treatment.

10:52:40 16 Q Theoretically would you find it useful if you could see
10:52:44 17 them more quickly than 12 weeks?

10:52:46 18 A No. A lot of drugs don't hit their maximum potency or
10:52:51 19 the patients may not be adherent. Remember, I'm trying to get
10:52:56 20 them to stay on therapy long-term.

10:52:57 21 So whether or not they're successful at four weeks
10:53:00 22 or six weeks is totally irrelevant to the long game, and as
10:53:04 23 the guidelines talk about, you need to monitor them every 4 to
10:53:08 24 12 months for lifetime to make sure that they stay on therapy.

10:53:12 25 So I'm interested more in a long-term follow-up than

10:53:16 1 an acute follow-up for my patients who have chronic diseases.

10:53:20 2 Q When you prescribe Vascepa, how much of a supply do you
10:53:23 3 write the prescription for?

10:53:25 4 A Yeah, so most commonly I prescribe a 3-month supply at
10:53:30 5 once. So I will give them 360 tablets, and then I will give
10:53:37 6 them three refills so that will cover one year of treatment
10:53:41 7 with Vascepa. That's how I implement Vascepa most commonly
10:53:46 8 when I first start it for a patient.

10:53:47 9 Q Do you intend for the patients to take the entire supply
10:53:51 10 as directed?

10:53:52 11 A Yes. It's always my hope that they comply or are
10:53:58 12 adherent with my recommendations.

10:53:59 13 Q Do you ever tell a patient to stop taking Vascepa before
10:54:03 14 the end of their supply?

10:54:04 15 A The only time I would ever stop it, and it would never be
10:54:07 16 my intent to not have them take a long-term treatment for a
10:54:12 17 chronic disease, but the only time I would sell them to stop
10:54:15 18 it is if they had an adverse event from that therapy.

10:54:21 19 So, for example, with Vascepa, if they developed a
10:54:21 20 bleeding problem, where they developed atrial fibrillation or
10:54:24 21 some other problem that we know could be related to Vascepa, I
10:54:27 22 might have them stop the therapy and come in and see me to
10:54:30 23 make sure that they're not suffering an adverse event from
10:54:34 24 taking that therapy.

10:54:35 25 Q Do you understand that the other asserted claims in this

10:54:37 1 case have the same or similar language concerning
10:54:41 2 administration for at least 12 weeks?

10:54:43 3 A Yes.

10:54:44 4 MR. M. KENNEDY: Mr. Brooks, could we pull up
10:54:47 5 PDX 2-14.

10:54:47 6 BY MR. M. KENNEDY:

10:54:50 7 Q And are these the other variations of the 12 weeks term
10:54:54 8 in the other asserted claims?

10:54:56 9 A Yes.

10:54:57 10 Q Do the opinions you've expressed today concerning the
10:55:01 11 claim element for a period of 12 weeks in the '728 patent
10:55:06 12 claim 1 apply with equal force to the same or similar elements
10:55:10 13 in the other asserted claims in this case?

10:55:12 14 A Yes.

10:55:13 15 Q And we've generally been asking -- I've generally been
10:55:16 16 asking you about the Vascepa label today. Do the opinions
10:55:19 17 you've expressed concerning the 12-week claim elements apply
10:55:23 18 with equal force to the Hikma and DRL proposed labels?

10:55:27 19 A Yes.

10:55:28 20 MR. M. KENNEDY: So, Your Honor, I'm moving on
10:55:30 21 to the next limitation. I'm happy to keep going, but I don't
10:55:33 22 know if it's about time for the morning break.

10:55:35 23 THE COURT: I think we already took the morning
10:55:42 24 break. I planned for us to go -- never mind. I guess it's
10:55:42 25 time for our morning break.

10:55:44 1 MR. M. KENNEDY: Yeah.

10:55:45 2 THE COURT: All right. We'll take our morning
10:55:48 3 break at this time.

10:55:49 4 MR. M. KENNEDY: Thank you, Your Honor.

11:07:14 5 (A recess was taken.)

11:21:09 6 THE COURT: Please be seated.

11:21:11 7 MR. M. KENNEDY: Your Honor, may I proceed?

11:21:14 8 THE COURT: Yes.

11:21:14 9 BY MR. M. KENNEDY:

11:21:16 10 Q Dr. Budoff, I actually do have one last question about
11:21:19 11 the 12-weeks claim elements.

11:21:21 12 So, if you typically prescribe a multimonth or even
11:21:25 13 a year supply to your patients -- strike that.

11:21:28 14 Why do you prescribe a multimonth or year-long
11:21:33 15 supply of Vascepa to your patients if the clinical study in
11:21:37 16 the label only has data for 12 weeks?

11:21:39 17 A Yes. So my intent is that they're going to stay on it
11:21:42 18 for life. The maximum I'm allowed to prescribe, at least in
11:21:46 19 the State of California, is for one year at a time so I give
11:21:49 20 them a full year, and then, as I'm seeing them back, I can
11:21:52 21 give them refills or give them new prescriptions after that.

11:21:58 22 Q Okay. Let's go -- Mr. Brooks, let's go PDX 2-15.

11:22:06 23 Moving on to the next claim element, the claim
11:22:09 24 element requiring administration to effect a reduction in
11:22:13 25 triglycerides.

11:22:14 1 Dr. Budoff, have you formed an opinion as to whether
11:22:18 2 the contents in the Vascepa label encourages clinicians to
11:22:21 3 administer Vascepa to effect a reduction in triglycerides as
11:22:25 4 required by claim 1 of the '728 Patent?

11:22:29 5 A Yes.

11:22:29 6 Q What is that opinion?

11:22:31 7 A That if physicians follow the label, that they will
11:22:34 8 effect a reduction in triglycerides and this limitation will
11:22:38 9 be met.

11:22:39 10 Q Have you been informed that the Court has construed the
11:22:42 11 claim language "to effect"?

11:22:44 12 A Yes.

11:22:44 13 Q Have prepared a slide reciting the Court's construction?

11:22:48 14 A Yes.

11:22:49 15 MR. M. KENNEDY: Mr. Brooks, let's half
11:22:52 16 PDX 2-16.

11:22:52 17 BY MR. M. KENNEDY:

11:22:54 18 Q And, Dr. Budoff, does this slide, PDX 2-16, state the
11:22:58 19 Court's construction?

11:22:59 20 A Yes.

11:23:02 21 Q And what's your understanding of this construction?

11:23:05 22 A That it's not only the intent, but that it actually has
11:23:07 23 to occur for the effect, the word effect.

11:23:11 24 Q And have you been informed the Court's also construed the
11:23:14 25 related language "compared to"?

11:23:16 1 A Yes.

11:23:17 2 Q And have you prepared a slide reciting that construction?

11:23:20 3 A Yes.

11:23:21 4 MR. M. KENNEDY: Mr. Brooks, could we please
11:23:23 5 have PDX 2-17.

11:23:23 6 BY MR. M. KENNEDY:

11:23:27 7 Q Does PDX 2-17 recite the Court's construction?

11:23:31 8 A Yes.

11:23:31 9 Q And what's your understanding of the Court's construction
11:23:35 10 of "compared to"?

11:23:35 11 A So it just means that the change will occur -- that the
11:23:45 12 change will occur and the magnitude of the change that will
11:23:49 13 occur.

11:23:49 14 Q Did you apply the constructions of "to effect" and
11:23:53 15 "compared to" in forming your opinions in this case?

11:23:55 16 A Yes.

11:23:56 17 MR. M. KENNEDY: So, Mr. Brooks, let's go back
11:23:58 18 to PDX 2-15.

11:23:58 19 BY MR. M. KENNEDY:

11:24:05 20 Q And how does the claim element regarding effecting a
11:24:08 21 reduction in triglycerides relate to the claim element
11:24:11 22 requiring.

11:24:12 23 "...compared to a second subject having a
11:24:15 24 fasting baseline triglyceride level of 500 milligrams
11:24:27 25 per deciliter to about 1500 milligrams per deciliter

11:24:31 1 who has not received the pharmaceutical composition
11:24:34 2 and a concurrent lipid-altering therapy,"
11:24:37 3 what's your understanding of how those two elements relate to
11:24:41 4 each other?

11:24:42 5 A So this is basically describing what -- the clinical
11:24:45 6 trial section showing that there was a second subject, and we
11:24:48 7 have a comparison in how well the Vascepa worked relative to a
11:24:53 8 second subject.

11:24:54 9 MR. M. KENNEDY: So, Mr. Brooks, can we put this
11:24:56 10 slide alongside the clinical study section in the Vascepa
11:25:00 11 label that we've looked at today.

11:25:02 12 And, Mr. Brooks, if you could go to section 14
11:25:15 13 of the Vascepa label, and if we could get the whole --
11:25:15 14 BY MR. M. KENNEDY:

11:25:21 15 Q So, Dr. Budoff, does the clinical study section of the
11:25:24 16 Vascepa label relate to your opinions concerning the "to
11:25:29 17 effect a reduction in triglycerides" claim element?

11:25:31 18 A Yes.

11:25:31 19 Q How so?

11:25:33 20 A Oh, the primary results that are presented here in label
11:25:37 21 two is the difference column, and the difference is comparing
11:25:43 22 Vascepa 4 grams with a second subject who is not being
11:25:46 23 treated, so, in this case, placebo therapy.

11:25:51 24 Q Does the clinical study section of the Vascepa label
11:25:54 25 reflect a reduction in triglycerides compared to a second

1 subject within the meaning of claim 1 of the '728 Patent?

2 A Yes. That difference of 33 percent is the reduction in
3 triglycerides compared to a second subject who is receiving
4 placebo, which is not receiving the pharmaceutical
5 composition.

6 MR. M. KENNEDY: Mr. Brooks, can we go to the
7 indications and usage section of the label, and you might as
8 well keep it alongside the slide.

9 BY MR. M. KENNEDY:

10 Q And, Dr. Budoff, does the second indication in the
11 Vascepa label relate to your opinions concerning the effect of
12 reduction in triglycerides claim element?

13 A Yes.

14 Q How so?

15 A So it says here as an adjunct to diet, so it's not
16 receiving concurrent lipid-altering therapy, just receiving
17 diet, so monotherapy in patients with severe
18 hypertriglyceridemia. In other words, patients who are --
19 have triglycerides above 500 milligrams per deciliter as
20 required in that element.

21 Q Do you prescribe Vascepa to your patients in accordance
22 with the label -- with the indication?

23 A Largely, yes.

24 Q Does the clinical study section of the label inform your
25 expectation of the lipid effects you achieve when you

1 prescribe Vascepa to your patients?

2 A Yes.

3 Q Why is that?

4 A So the -- I look towards the results that I'm expected to
5 get with therapy, so I use the clinical trial section to say
6 what would be my expected result, and then I see if my patient
7 achieved that average result that was seen in the trial, and,
8 if not, then I have to make changes in their regimen.

9 Q What percentage of your patients who you prescribe
10 Vascepa experience lipid effects such as TG reduction in line
11 with the results recited in the labeling?

12 A Yes, so about three quarters of patients will be at or
13 around that number. So it's not going to be exactly minus
14 33.0 percent, but they will have generally about a one-third
15 reduction.

16 Of the remaining 25 percent, half of those patients
17 will have even more dramatic effects, and half of those
18 patients will have less dramatic effects. That's just what we
19 call the normal distribution of results when we treat enough
20 patients.

21 Q When you write a prescription to a patient with severe
22 hypertriglyceridemia for Vascepa, do you have any way of
23 knowing whether they're going to achieve lipid effects in line
24 with the MARINE label as opposed to being one the people who
25 don't?

11:28:47 1 A No, there's no good way to know in advance. That's why
11:28:52 2 we repeat the lipid value at 12 weeks to see did they -- did
11:28:56 3 they achieve or did they not achieve those desired results.

11:28:59 4 Q What lipid effects do you expect from a given SHT patient
11:29:05 5 when you write the prescription?

11:29:07 6 A So I hope, I anticipate, I plan that they will achieve a
11:29:11 7 33 percent reduction in triglycerides and that their LDL will
11:29:15 8 not go up. So, that is my goal and intent when I'm
11:29:20 9 prescribing this therapy.

11:29:21 10 I anticipate that the apo B will go down. I know
11:29:28 11 we'll talk about that later. But I think that those are my
11:29:30 12 goals and intent.

11:29:31 13 And then -- but some patients don't -- don't fall
11:29:35 14 into that category, and they have to be -- I have to adjust my
11:29:39 15 treatment based on the actual results in that individual
11:29:41 16 patient.

11:29:42 17 Q Are you aware that the other asserted claims in this case
11:29:45 18 also have claim elements relating to effecting a reduction in
11:29:50 19 triglycerides?

11:29:50 20 A Yes.

11:29:50 21 Q Have you prepared a slide reciting those same or similar
11:29:54 22 limitations in the other asserted claims?

11:29:56 23 A Yes.

11:29:57 24 MR. M. KENNEDY: Mr. Brooks, could we have
11:29:59 25 PDX 2-18.

11:29:59 1 BY MR. M. KENNEDY:

11:30:02 2 Q Does PDX 2-18 recite the other claim elements relating to
11:30:07 3 effecting a reduction in triglycerides?

11:30:10 4 A Yes.

11:30:12 5 Q And you also have some notations on the right-hand side
11:30:16 6 concerning comparisons of various types. What does that
11:30:20 7 denote?

11:30:20 8 A So those are the different languages that are used in
11:30:23 9 each of the different claims.

11:30:25 10 So sometimes the language is "to effect a reduction
11:30:31 11 in triglycerides compared to a second subject," we just
11:30:35 12 described that, that's the placebo-controlled arm of the
11:30:39 13 MARINE trial.

11:30:41 14 Sometimes it says "compared to placebo control,"
11:30:44 15 that's another way of saying a second subject not receiving
11:30:44 16 active compound.

11:30:49 17 Sometimes it says "compared to baseline" or "in the
11:30:52 18 subject," and those would imply just looking at the reductions
11:30:57 19 in line with the -- per the individual and not comparing it to
11:31:01 20 a second subject or a placebo control.

11:31:05 21 MR. M. KENNEDY: Mr. Brooks, can we put table 2
11:31:07 22 back up alongside this slide, and maybe blow up the table?

11:31:07 23 BY MR. M. KENNEDY:

11:31:15 24 Q So, Dr. Budoff, does table 2 of the Vascepa label reflect
11:31:19 25 that administration of Vascepa effects a reduction in fasting

1 triglycerides of at least about ten percent in the subject?

2 A Yes, the average reduction is 33 percent. For compared
3 to a second subject or placebo control, the average drop is
4 27 percent in the same subject or compared to baseline, and
5 both minus 27 and minus 33 are more than a 10 percent drop.

6 Q And let me ask you the same question with respect to the
7 limitation effects reduction in fasting triglycerides of at
8 least about 20 percent compared to placebo control as required
9 by the '560 patent claim 17.

10 A Yes. Both minus 27 percent and minus 33 percent are at
11 least 20 percent, so that claim element would also be met.

12 Q And then, finally, does table 2 of the Vascepa label
13 reflect that administration of Vascepa according to the label
14 would achieve a statistically significant reduction in
15 triglycerides in the subject as required by claim 4 of the
16 '715 Patent?

17 A Yes, if you see where it says minus 33 percent, and you
18 see the asterisk that says the P value is less than .001, so
19 that is highly statistically significant change, so that would
20 achieve an effect that is a statistically significant
21 reduction in triglycerides.

22 MR. M. KENNEDY: Mr. Brooks, could we go to
23 PDX 2-19.

24 BY MR. M. KENNEDY:

25 Q Now we're back on claim 1 of the '728 Patent, and I would

1 like to turn to the element regarding avoiding a reduction in
2 LDL-C.

3 Have you formed an opinion concerning whether the
4 Vascepa label encourages clinicians to prescribe the product
5 described in the label to effect a reduction in triglycerides
6 without substantially increasing LDL-C compared to a second
7 subject within the meaning of claim 1 of the '728 patent?

8 A Yes.

9 Q What is that opinion?

10 A That we have seen from the MARINE trial, and we have
11 discussed already, that the LDL cholesterol does not go up, it
12 goes down by minus 2 percent, so that is not substantially
13 increasing LDL, that is neutral or slightly decreasing LDL.

14 Q And to recap, when claim 1 of the '728 refers to a
15 comparison to a second subject, what does that comparison
16 correspond to in table 2 of the Vascepa label?

17 A So that would be the placebo column. So that would be
18 looking at the difference between the active Vascepa minus the
19 placebo column to get the net difference which, in the MARINE
20 trial, was minus 2 percent change in LDL cholesterol.

21 Q So you understand the Court's construed the language
22 "without substantially increasing LDL-C"?

23 A Yes.

24 Q Do you have a slide showing that construction?

25 A Yes.

11:34:25 1 MR. M. KENNEDY: And, Mr. Brooks, can we have
11:34:27 2 PDX 2-20.

11:34:27 3 BY MR. M. KENNEDY:

11:34:30 4 Q Dr. Budoff, does this slide, PDX 2-20, recite the Court's
11:34:35 5 construction of "without substantially increasing LDL-C"?

11:34:41 6 A Yes.

11:34:41 7 Q And you see the construction is "without a meaningful
11:34:43 8 increase in LDL-C." What does clinically meaningful mean in
11:34:46 9 this context?

11:34:47 10 A So clinically meaningful in clinical practice, and this
11:34:51 11 was brought out yesterday as well, is a 6 percent rise.
11:34:55 12 That's typically considered a meaningful increase in LDL
11:34:59 13 cholesterol whereby we might have to react to it, and that
11:35:02 14 makes it a clinical event that I have to then react to that 6
11:35:07 15 percent rise by changing my underlying management.

11:35:10 16 Q Did you apply the construction, the Court's construction
11:35:14 17 of "without substantially increasing LDL-C" in forming your
11:35:18 18 opinions?

11:35:19 19 A Yes.

11:35:19 20 Q And then there's the related construction that appears in
11:35:22 21 different asserted claims, "without effecting a statistically
11:35:26 22 significant increase in LDL-C." What's your understanding of
11:35:31 23 that construction that's recited on the slide?

11:35:32 24 A Yes. So that, again, is -- basically, our definition of
11:35:36 25 statistically significant is that it's not -- it's unlikely to

1 have occurred due to chance and that it's a real change.

2 MR. M. KENNEDY: Mr. Brooks, can we go to the
3 dosage and administration section of the Vascepa label.

4 BY MR. M. KENNEDY:

5 Q And, Dr. Budoff, I would like to direct you in particular
6 to 2.1 where it says, "assess lipid levels before initiating
7 therapy." Do you see that?

8 A Yes.

9 Q Does this relate to whether Vascepa avoids an LDL-C
10 increase?

11 A Well, yes. So, I mean, it doesn't say to address the
12 triglyceride levels, or assess triglyceride levels before
13 initiating therapy, it says lipid levels, and that tells the
14 clinician to get a full lipid panel, and a full lipid panel
15 includes LDL cholesterol as well as triglycerides.

16 So it's reminding the physician to get the full
17 panel so that you can see what the effect is, not only on
18 triglycerides, but also on LDL cholesterol.

19 Q Do clinicians treating STG patients typically get these
20 lipid panels?

21 A Yes. It's very standard to get a standard lipid panel in
22 all of your patients. I don't know how you would prescribe
23 any cholesterol-lowering medicine without assessing a lipid
24 panel before initiating therapies.

25 So I think this is fairly standard language for any

1 drug in this general class of lipid metabolism.

2 MR. M. KENNEDY: So, Mr. Brooks, can we pull up
3 PDX 2-19 and put it alongside table 2.

4 BY MR. M. KENNEDY:

5 Q And is there anything in the clinical study section of
6 the Vascepa label that speaks to whether the label encourages
7 administration of Vascepa to effect a reduction in
8 triglycerides without substantially increasing LDL-C compared
9 to a second subject?

10 A Yes, so in the LDL-C column on the far right is compared
11 to a second subject or compared to placebo control, and that's
12 minus two percent.

13 So you can see LDL-C went down by 2 percent, which
14 is not a substantial increase or meaningful increase because
15 it's a decrease.

16 Q And the second -- the -- where, in the clinical study
17 section, does it reflect a comparison to a second subject in
18 the way required by claim 1 of the '728 Patent?

19 A I mean, literally, right under the table there it says
20 difference, and it says the median of Vascepa minus placebo.
21 So it literally defines that it's comparing it to the second
22 subject.

23 It also says it in the last sentence of the
24 paragraph, the reduction in triglycerides observed with
25 Vascepa was not associated with elevations in LDL-C levels

1 relative to placebo.

2 Q Why is that relevant?

3 A Well, they're calling that out to the clinician. This is
4 an emphasis to the clinician that this is an important
5 finding, and thus it's put in the table -- it's put in the
6 text below the table to further emphasize that result.

7 Q Do the effects on LDL-C shown in table 2 influence your
8 treatment decisions for SH -- STG patients?

9 A Yes, I think as we talked about before, the other agents
10 in the class that are indicated to reduce severe
11 hypertriglyceridemia, niacin, fibrates, and Lovaza, are all
12 associated with significant increases in LDL cholesterol.

13 This drug is not associated with elevations in LDL
14 cholesterol making it a unique opportunity to treat patients
15 for their triglycerides without increasing their cardiac risk
16 of having a heart attack downstream.

17 Q So let me ask a slightly broader question not limited to
18 LDL-C effects, but also for the other lipid effects shown in
19 table 2.

20 Do they -- the clinical data on table 2 influence
21 clinicians' treatment decisions for their severely
22 hypertriglyceridemic patients?

23 A Yes.

24 Q How -- why is that?

25 A So, again, triglycerides go down significantly, LDL does

1 not go up.

2 And what we haven't yet talked about, but I think is
3 also important, is that apo B -- remember apolipoprotein B is
4 the bad lipoprotein, actually goes down significantly.

5 So it has three affects that are all deemed positive
6 for our patients with severe hypertriglyceridemia.

7 MR. M. KENNEDY: Mr. Brooks, can we go to the
8 warnings and precautions section of the Vascepa label.

9 BY MR. M. KENNEDY:

10 Q And, Dr. Budoff, is there anything in the warnings and
11 precautions section of the Vascepa label that is relevant to
12 your opinion that the label encourages administration to
13 effect a reduction in triglycerides without substantially
14 raising LDL-C?

15 A Yes.

16 Q What about this section supports that opinion?

17 A So, in all the other therapies, the fibrates, Lovaza,
18 there is a warning about LDL rise in the warnings and
19 precautions sections of those labels.

20 Here there is no such warning, and a doctor who is
21 treating severe hypertriglyceridemia would know that. This
22 would be a common knowledge of the effects of the other agents
23 and the warnings that go with the other agents, and so the
24 absence of that warning is important for physicians to
25 understand.

11:41:56 1 Q Do you understand that the other asserted -- some of the
11:42:01 2 other asserted claims in this case have limitations drawn to
11:42:04 3 avoiding LDL-C effects?

11:42:07 4 A Yes.

11:42:08 5 MR. M. KENNEDY: Mr. Brooks, could we have
11:42:10 6 PDX 2-21.

11:42:10 7 BY MR. M. KENNEDY:

11:42:14 8 Q Dr. Budoff, does this slide depict the other claim
11:42:18 9 elements and other asserted claims regarding LDL-C effects?

11:42:22 10 A Yes.

11:42:23 11 Q And, again, the different claims have different
11:42:26 12 comparators such as second subject, placebo control, and
11:42:28 13 baseline?

11:42:29 14 A Yes.

11:42:29 15 Q Do the opinions you've expressed today concerning the
11:42:32 16 claim element, "without substantially increasing LDL-C" in
11:42:37 17 claim 1 of the '728 Patent, apply with equal force to the same
11:42:41 18 or similar terms in the other asserted claims?

11:42:44 19 A Yes.

11:42:45 20 Q For example, does -- does the Vascepa label reflect
11:42:52 21 avoidance of a statistically significant increase in LDL-C in
11:42:59 22 the subject as required by '715 patent, claim 14 patent?

11:43:02 23 A Yes, there was a decrease in LDL-C so there was not a
11:43:06 24 statistically significant increase by definition.

11:43:10 25 Q So does that entail that the terms about avoiding an

1 increase this LDL-C in claims 4 and 17 of the '560 patent are
2 also met?

3 A Yes. Again, a decrease is without an increase by
4 definition. So I think that those claims are all met by the
5 results of the clinical trials section that's put forth in all
6 of the labels.

7 MR. M. KENNEDY: Could we go to the slide
8 PDX 2-22.

9 BY MR. M. KENNEDY:

10 Q Dr. Budoff, do you have an opinion as to whether the
11 Vascepa label encourages physicians to prescribe Vascepa to
12 severely hypertriglyceridemic patients who are not receiving a
13 concurrent lipid-altering therapy as required by claim 1 of
14 the '728 Patent?

15 A Yes.

16 Q What is that opinion?

17 A That the majority of patients treated in the MARINE trial
18 and the indication itself both advocate for monotherapy.
19 Monotherapy by definition is without receiving concurrent
20 lipid-altering therapy.

21 Q Do you understand that the Court previously construed the
22 phrase "concurrent lipid-altering therapy"?

23 A Yes.

24 MR. M. KENNEDY: Mr. Brooks, could we have
25 PDX 2-23.

11:44:40 1 BY MR. M. KENNEDY:

11:44:44 2 Q And, Dr. Budoff, is this the Court's construction?

11:44:46 3 A Yes.

11:44:47 4 Q Did you apply the Court's construction of "concurrent
11:44:51 5 lipid-altering therapy" in forming your opinions in this case?

11:44:54 6 A Yes.

11:44:55 7 MR. M. KENNEDY: Mr. Brooks, can we go to trial
11:45:00 8 Exhibit 1186, the Vascepa label, the indications and usage
11:45:00 9 section.

11:45:00 10 BY MR. M. KENNEDY:

11:45:06 11 Q And, Dr. Budoff, is there anything about the indications
11:45:10 12 and usage that is relevant to your opinion that the label
11:45:14 13 encourages administration to severely hypertriglyceridemic
11:45:20 14 patients who aren't receiving concurrent lipid-altering
11:45:24 15 therapy?

11:45:25 16 A Yes.

11:45:25 17 Q What -- what about the indications and usage section
11:45:28 18 supports your opinion?

11:45:29 19 A So you can see the MARINE indication literally says as an
11:45:34 20 adjunct to diet to reduce triglyceride levels. So diet is not
11:45:39 21 considered concurrent lipid-altering therapy. The Court
11:45:43 22 construed that that's a medication.

11:45:45 23 So this is literally advocating for Vascepa to be
11:45:51 24 used as monotherapy without concurrent -- it's not requiring
11:45:56 25 concurrent lipid-altering therapy.

11:45:59 1 Q Do you -- so with respect to your severe
11:46:03 2 hypertriglyceridemic patients, do you sometimes prescribe
11:46:07 3 concurrent lipid-altering therapy and sometimes not?

11:46:11 4 A Yes.

11:46:12 5 Q Could you describe the type of patient who has severe
11:46:15 6 hypertriglyceridemia to whom you would prescribe Vascepa as a
11:46:18 7 monotherapy?

11:46:19 8 A Yeah. So a very common scenario is -- and triglycerides
11:46:24 9 tend to affect women more than men, hypertriglyceridemia.

11:46:29 10 So a very common scenario would be a young,
11:46:33 11 otherwise healthy woman gets referred to me because their
11:46:37 12 triglycerides are very high.

11:46:38 13 When I meet her, I ask her questions about her diet
11:46:41 14 and exercise. She's already adhering to a good diet, she's
11:46:45 15 already exercising regularly. I can see that she's not very
11:46:49 16 overweight so I know she's an over -- overwhelmingly healthy
11:46:55 17 person.

11:46:57 18 I check for diabetes and thyroid disease, and if she
11:47:00 19 doesn't have any of those things, then my primary therapy is
11:47:03 20 going to be Vascepa. She's on it, it's an adjunct to diet and
11:47:07 21 exercise.

11:47:08 22 Now I'm going to prescribe Vascepa monotherapy.
11:47:11 23 After I prescribe monotherapy, I'll see her back, and I'll
11:47:15 24 assess her lipid profile in three months.

11:47:18 25 But a lot of these young, healthy people only have

11:47:20 1 triglyceride abnormalities. Her LDL cholesterol could be nice
11:47:28 2 and low, and if her LDL cholesterol is nice and low, and she's
11:47:31 3 otherwise healthy, then she doesn't qualify for concurrent
11:47:33 4 lipid-altering therapy. I don't need to put her on a statin,
11:47:37 5 she wouldn't benefit from such therapy, and I would just
11:47:40 6 continue Vascepa monotherapy in that patient.

11:47:43 7 Q Is there anything about the Vascepa labeling that gives
11:47:45 8 you comfort that Vascepa would be appropriate as a monotherapy
11:47:49 9 in the patient you just described?

11:47:51 10 A Yes.

11:47:51 11 Q What -- what part of the label?

11:47:53 12 A So the clinical trial section also speaks to the utility
11:47:58 13 of this therapy as monotherapy.

11:48:00 14 Q Could you describe the type of severely
11:48:04 15 hypertriglyceridemic patient that you might prescribe Vascepa
11:48:08 16 along with a concurrent lipid-altering therapy?

11:48:13 17 A Yes. So take another patient walks into my office, this
11:48:16 18 time they have underlying heart disease so they might have
11:48:22 19 already suffered a heart attack or maybe have a stint. Their
11:48:26 20 triglycerides are over 500.

11:48:28 21 I implement diet and exercise, have them come back.
11:48:32 22 They're still above 500. I now need to use Vascepa therapy in
11:48:39 23 that person.

11:48:39 24 They might already be on a statin, so that would be
11:48:43 25 concurrent lipid-altering therapy or, after I put them on

11:48:47 1 Vascepa and see that their LDL, their bad cholesterol, is
11:48:52 2 still too high, I would then implement statin therapy.

11:48:57 3 We discussed the guidelines advocate for that
11:49:00 4 step-wise care that is so important when we assess patients
11:49:04 5 with high triglycerides.

11:49:07 6 MR. M. KENNEDY: Mr. Brooks, could we go to
11:49:10 7 table 2.

11:49:10 8 BY MR. M. KENNEDY:

11:49:14 9 Q So is there anything about the labeling that encourages
11:49:17 10 you as a clinician to administer Vascepa -- I'll start -- I'll
11:49:22 11 just start without concurrent lipid-altering therapy, the
11:49:27 12 young woman, for example.

11:49:28 13 A Yes. Mr. Brooks, could you expand it to the top
11:49:30 14 paragraph real quickly? Sorry.

11:49:33 15 So this is the full clinical trial section, and you
11:49:36 16 can see there's a sentence fairly far down in the first
11:49:40 17 paragraph starting with 25 percent of patients were on
11:49:44 18 concomitant statin therapy.

11:49:47 19 So that literally tells you that this -- this trial,
11:49:51 20 one fourth of the patients were on a statin plus Vascepa, or
11:49:59 21 statin plus placebo, and 75 percent were not.

11:50:02 22 So the vast majority of the patient results in table
11:50:06 23 2 reflects Vascepa monotherapy. That literally reflects
11:50:11 24 75 percent of the results of the patients randomized in this
11:50:15 25 trial.

1 So the study definitely encourages physicians to
2 prescribe Vascepa as monotherapy, and because 25 percent of
3 patients were on statin, concomitant statin therapy, it also
4 encourages patients to use it with concurrent lipid-altering
5 therapy when appropriate.

6 Q I'd like to look at the verbiage underneath table 2. Is
7 there anything about that portion of the clinical study
8 section that encourages clinicians to administer Vascepa
9 without concurrent lipid-altering therapy?

10 A Well, again, so two-thirds, three-quarters of the
11 patients achieve these results without statin therapy. So
12 this largely reflects Vascepa reduced triglycerides with
13 without elevating LDL-C, that largely reflects the placebo,
14 the statin -- I mean, the Vascepa monotherapy arm rather than
15 patients who are on concomitant therapy.

16 Q Do you understand that some the other asserted claims
17 have the same or similar claim language concerning
18 administering Vascepa to STG patients without concurrent
19 lipid-altering therapy?

20 A Yes.

21 MR. M. KENNEDY: Let's look at PDX 2-24.

22 BY MR. M. KENNEDY:

23 Q Dr. Budoff, does this slide, PDX 2-24, recite the other
24 similar claim language?

25 A Yes.

11:51:44 1 Q Do the opinions you've expressed today concerning the
11:51:47 2 claim language "who does not receive concurrent lipid-altering
11:51:52 3 therapy" in claim 1 of the '728 Patent apply with equal force
11:51:56 4 to the same or similar claim elements in the other asserted
11:52:00 5 claims that have these limitations?

11:52:01 6 A Yes.

11:52:02 7 Q And, again, the opinions -- when you've answered
11:52:05 8 questions about the Vascepa label, do your opinions concerning
11:52:08 9 the concurrent lipid-altering therapy claim elements apply
11:52:12 10 with equal force to the Hikma and DRL labels?

11:52:15 11 A Yes.

11:52:16 12 MR. M. KENNEDY: So, Mr. Brooks, can we go to
11:52:18 13 PDX 2-26.

11:52:18 14 BY MR. M. KENNEDY:

11:52:23 15 Q And I would like to do the last two elements of this
11:52:25 16 patent together. These require administering orally to the
11:52:31 17 subject about 4 grams per-day of a pharmaceutical composition.

11:52:36 18 Have you formed any opinions concerning whether the
11:52:39 19 Vascepa label encourages clinicians to administer orally to
11:52:44 20 the subject about 4 grams per day of a pharmaceutical
11:52:48 21 composition as required in claim 1 of the '728 Patent?

11:52:51 22 A Yes.

11:52:52 23 Q What is that opinion?

11:52:53 24 A Multiple times throughout the patent physicians are
11:52:56 25 encouraged to administer this medicine. The only way it can

11:53:00 1 be administered is orally, and the only dose is 4 grams per
11:53:05 2 day, so these two are automatically met by using the
11:53:08 3 prescription the way it has to be prescribed.

11:53:11 4 Q So I think in your last answer you said the patent
11:53:15 5 requires, did you mean the prescribing --

11:53:17 6 A The label requires.

11:53:18 7 Q So do you understand the Court previously construed the
11:53:24 8 orally -- the "administering orally" claim language?

11:53:27 9 A Yes.

11:53:28 10 MR. M. KENNEDY: And, Mr. Brooks, can we go to
11:53:30 11 PDX 2-27.

11:53:30 12 BY MR. M. KENNEDY:

11:53:34 13 Q And, Dr. Budoff, is this the construction you applied in
11:53:38 14 forming your opinions?

11:53:40 15 A Yes.

11:53:40 16 Q And so what's your understanding of the Court's
11:53:43 17 construction of "orally administered" or "administering"?

11:53:47 18 A That the doctor is the one prescribing the medicine, and
11:53:50 19 the medication is being taken by the patient at the doctor's
11:53:53 20 direction. So this is a doctor-directed oral administration.

11:53:57 21 Q So writing the prescription constitutes administering?

11:54:02 22 A Yes.

11:54:02 23 Q And do you understand the parties also reached an
11:54:05 24 agreement about the construction the claim term
11:54:08 25 "pharmaceutical composition"?

11:54:11 1 A Yes.

11:54:11 2 MR. M. KENNEDY: And, Mr. Brooks, can we have
11:54:13 3 2-30.

11:54:13 4 BY MR. M. KENNEDY:

11:54:17 5 Q And, Dr. Budoff, do you see the stipulated construction
11:54:21 6 of "pharmaceutical composition"?

11:54:24 7 A Yes.

11:54:24 8 Q Is this the construction you applied in forming your
11:54:27 9 opinions?

11:54:27 10 A Yes.

11:54:29 11 MR. M. KENNEDY: Mr. Brooks, could we go back to
11:54:32 12 slide 2-26 and put it alongside the description section of the
11:54:39 13 prescribing information, section 11.

11:54:39 14 BY MR. M. KENNEDY:

11:54:45 15 Q And, Dr. Budoff, I don't think we've seen this section of
11:54:48 16 the labeling today. In general, what's the purpose of the
11:54:50 17 description section of a label?

11:54:52 18 A This describes the medication so that the physician knows
11:54:56 19 and the patient knows what it's going to look like and how --
11:54:59 20 what it constitutes.

11:55:00 21 Q And do the Hikma and DRL labels contain identical
11:55:08 22 descriptions?

11:55:08 23 A Yes.

11:55:09 24 Q Except they're not called Vascepa, they're called
11:55:12 25 icosapent ethyl.

11:55:13 1 A Yes.

11:55:13 2 Q So what in the description section informs your opinion
11:55:17 3 that the label encourages administration orally to the subject
11:55:21 4 about 4 grams per-day of a pharmaceutical composition?

11:55:26 5 A Well, the description says it's for oral use.

11:55:29 6 Q And what does it say about 4 grams?

11:55:32 7 A I don't think it says 4 grams here. I think in the
11:55:35 8 dosage and administration section it speaks to 4 grams as the
11:55:39 9 dose that's to be given.

11:55:42 10 MR. M. KENNEDY: So let's go to the dosage and
11:55:44 11 administration section.

11:55:44 12 BY MR. M. KENNEDY:

11:55:47 13 Q And what about the dosage and administration section of
11:55:50 14 the Vascepa label informs your opinion that the label
11:55:55 15 encourages administering about 4 grams per day of a
11:55:57 16 pharmaceutical composition?

11:56:00 17 A Under 2.2, dosage and administration, the daily dose of
11:56:03 18 Vascepa is 4 grams per day, and then advise patients to
11:56:07 19 swallow whole and take it with food.

11:56:11 20 Both of those imply -- the only way you can swallow
11:56:14 21 it or take it with food is an oral administration. So this
11:56:14 22 covers both oral and 4 grams.

11:56:20 23 Q And what does the dosage and administration section say
11:56:22 24 about the dosage form in which Vascepa is delivered?

11:56:27 25 A So it's a capsule, so, again, given orally.

11:56:30 1 Q And are you aware that other claims at issue in this case
11:56:33 2 have language similar to about 4 grams per day that appears in
11:56:38 3 claim 1 of the '728 Patent?

11:56:40 4 A Yes.

11:56:41 5 MR. M. KENNEDY: And can we go to slide
11:56:43 6 two-dash, PDX 2-31? PDX 2-31? Oh, sorry.

11:56:43 7 BY MR. M. KENNEDY:

11:57:00 8 Q And, Dr. Budoff, do the opinions you've expressed today
11:57:04 9 concerning the about 4 grams per day claim element in claim 1
11:57:08 10 of the '728 Patent apply with equal force to the same or
11:57:12 11 similar claim elements in the other asserted claims?

11:57:14 12 A Yes.

11:57:15 13 MR. M. KENNEDY: And then, Mr. Brooks, if we
11:57:17 14 could go to PDX 2-28.

11:57:17 15 BY MR. M. KENNEDY:

11:57:26 16 Q And do you understand that other claims at issue in this
11:57:27 17 case have the same or similar language concerning
11:57:31 18 administering orally to the subject?

11:57:34 19 A Yes.

11:57:34 20 Q And do the opinions you've expressed today concerning
11:57:37 21 whether the Vascepa label encourages administering orally to
11:57:41 22 the subject as required of claim 1 of the '728 Patent apply
11:57:45 23 with equal force to the other asserted claims with the same or
11:57:49 24 similar claim language?

11:57:50 25 A Yes.

11:57:52 1 MR. M. KENNEDY: So, Mr. Brooks, can we go to
11:58:00 2 PDX 2-32. And you can take down the label for right now.
11:58:02 3 Thank you.

11:58:02 4 BY MR. M. KENNEDY:

11:58:03 5 Q And just so sum up, Dr. Budoff, what is your opinion
11:58:06 6 concerning whether the Vascepa label taken as a whole will
11:58:09 7 encourage clinicians to admit to follow each step in the
11:58:13 8 method claimed by claim 1 of the '728 Patent?

11:58:17 9 A Yes. So as I've just outlined, every element will be
11:58:22 10 met, every limitation will be met, if physicians follow the
11:58:26 11 label, they will be encouraged to do all of these steps that
11:58:29 12 are listed here on the slide.

11:58:31 13 Q In your opinion, would physicians follow the label?

11:58:34 14 A Yes, physicians are supposed to follow the label.

11:58:37 15 Q And, again, if I had asked you about the Hikma or DRL
11:58:40 16 label instead of the Vascepa label, would your opinions be the
11:58:44 17 same?

11:58:44 18 A Yes.

11:58:44 19 MR. M. KENNEDY: So let's move on to claim 16 of
11:58:47 20 the '728 Patent, and that's PDX 2-33.

11:58:47 21 BY MR. M. KENNEDY:

11:58:51 22 Q And, Dr. Budoff, what are you depicting on this slide?

11:58:55 23 A So this is just the other claim that's -- that's being
11:59:00 24 contested, and it just shows that all the claim elements are
11:59:05 25 met in claim 1.

11:59:07 1 So that refers to the previous slide that we just
11:59:11 2 went through, all the limitations are already met, and then it
11:59:14 3 describes another -- the pharmaceutical composition again
11:59:17 4 which has already been stipulated or agreed upon by the
11:59:20 5 parties. So all the elements for claim 16 of the '728 Patent
11:59:29 6 are met.

11:59:29 7 Q So just to sum up, would the labeling -- Vascepa labeling
11:59:33 8 encouraging -- encourage clinicians to follow each step of the
11:59:35 9 method claimed by claim 16 of the '728 Patent?

11:59:38 10 A Yes. For all the reasons I've previously stated,
11:59:42 11 physicians will -- following the label will meet all of these
11:59:45 12 elements.

11:59:45 13 Q And you would have the same opinion with respect to the
11:59:48 14 Hikma and DRL labels?

11:59:50 15 A Yes.

11:59:51 16 MR. M. KENNEDY: So let's move on to trial
11:59:53 17 Exhibit 26.

11:59:53 18 BY MR. M. KENNEDY:

11:59:57 19 Q And, Dr. Budoff, do you recognize that document?

11:59:59 20 A Yes.

11:59:59 21 Q What is it?

12:00:00 22 A This is the '652 Patent.

12:00:03 23 Q And so that's U.S. patent 8,367,652?

12:00:07 24 A Yes.

12:00:07 25 Q Is this one of the patents you've analyzed in forming

12:00:11 1 your opinions in this case?

12:00:11 2 A Yes.

12:00:13 3 MR. M. KENNEDY: Your Honor, I believe PX 26 is
12:00:16 4 on the pre-admitted exhibit list.

12:00:18 5 THE CLERK: It is.

12:00:19 6 THE COURT: Thank you.

12:00:19 7 BY MR. M. KENNEDY:

12:00:21 8 Q And you understand that Amarin is asserting infringement
12:00:24 9 of claim 1 of the '652 Patent?

12:00:27 10 A Yes.

12:00:27 11 MR. M. KENNEDY: So, Mr. Brooks, let's just go
12:00:28 12 to PDX 2-34.

12:00:28 13 BY MR. M. KENNEDY:

12:00:33 14 Q And, Dr. Budoff, what are you attempting to state here
12:00:38 15 where you have the notation "See Claim 1 ('728 Patent)"?

12:00:42 16 A So these are the same or similar languages that we've
12:00:46 17 already discussed and demonstrated, that a physician following
12:00:50 18 the label will meet all of these limitations. So the same
12:00:56 19 analysis that I applied to claim 1 of the '728 Patent applies
12:01:01 20 to claim 1 of the '652 Patent.

12:01:04 21 Q Now, there's one element that's not filled in here,
12:01:08 22 "compared to baseline." Do you see that?

12:01:10 23 A Yes.

12:01:10 24 Q Have you formed any opinions concerning whether the
12:01:14 25 Vascepa label encourages clinicians to prescribe Vascepa to a

12:01:18 1 subject to effect a reduction in triglycerides without
12:01:22 2 substantially increasing LDL-C compared to baseline as
12:01:27 3 required by claim 1 of the '652 Patent?

12:01:31 4 A Yes.

12:01:31 5 Q And what is that opinion?

12:01:32 6 A That they would be encouraged to lower triglycerides, and
12:01:38 7 LDL will not go up when you compare that person to their own
12:01:43 8 baseline, and that was done in the clinical studies section of
12:01:47 9 the labels.

12:01:48 10 MR. M. KENNEDY: And let's just very quickly put
12:01:50 11 this slide alongside table 2 of the Vascepa label.

12:01:50 12 BY MR. M. KENNEDY:

12:01:54 13 Q And, Dr. Budoff, if you could just point out, does the
12:01:59 14 MARINE data stated in the Vascepa label contain a comparison
12:02:02 15 to baseline?

12:02:03 16 A Yes. So in the table 2, can you see under Vascepa it
12:02:08 17 says the word baseline. These are the changes that are seen
12:02:13 18 compared to baseline.

12:02:15 19 So to effect a reduction in triglycerides, the
12:02:19 20 change was 27 percent compared to baseline. Two, without
12:02:23 21 increasing LDL-C, there was a minus five percent, there was
12:02:29 22 decrease in LDL-C compared to baseline. So these elements
12:02:33 23 will be met when physicians follow the label.

12:02:36 24 Q And when you administer Vascepa to a subject, what kinds
12:02:42 25 of lipid effects do you expect to see in that patient? I

1 should say a subject with severe hypertriglyceridemia.

2 A Right. So, again, our intent is, in our vast majority of
3 patients, that our patients will behave similarly to the
4 clinical trial, and these are the types of results that we
5 will see.

6 So we will see a significant reduction in
7 triglycerides with a small decrease or no change in LDL-C.

8 Q So, in your opinion, will the Vascepa labeling encourage
9 clinicians to follow each step in the method claimed in claim
10 1 of the '652 Patent?

11 A Yes.

12 MR. M. KENNEDY: So let's move on to Plaintiffs'
13 Exhibit 25?

14 BY MR. M. KENNEDY:

15 Q And, Dr. Budoff, do you recognize this document?

16 A Yes, this is U.S. patent 8,357,677.

17 Q Is this one of the patents you've analyzed in this case?

18 A Yes.

19 Q And have you been informed that Amarin is asserting
20 infringement of claims 1 and 8 of the '677 Patent?

21 A Yes.

22 MR. M. KENNEDY: Mr. Brooks, can we please go to
23 slide PDX 2-36.

24 BY MR. M. KENNEDY:

25 Q And, Dr. Budoff, again, can you just very briefly explain

12:03:57 1 what this slide shows.

12:03:58 2 A Yes. So for all the analyses that we've already
12:04:02 3 described for each of these claim elements, these are the same
12:04:05 4 or similar language to claim 1 of the '728 Patent, that these
12:04:10 5 elements will be met in claim 1 of the '677 Patent.

12:04:15 6 The only claim -- or, excuse me, the only element
12:04:19 7 that's not yet met in this is "compared to placebo control."

12:04:24 8 Q And have you formed any opinions concerning whether the
12:04:27 9 Vascepa label encourages clinicians to prescribe Vascepa to
12:04:32 10 effect a reduction in triglycerides without substantially
12:04:36 11 increasing LDL-C compared to placebo control as required by
12:04:42 12 claim 1 of the '677 Patent?

12:04:42 13 A Yes.

12:04:43 14 Q What is that opinion?

12:04:44 15 A So as we've talked about before, probably now a few
12:04:48 16 times, the net effect of following these elements or following
12:04:54 17 the label and prescribing Vascepa the way that the label
12:04:59 18 encourages, will effect a reduction in triglycerides on
12:05:02 19 average by 33 percent compared to placebo control, and will
12:05:08 20 lower LDL-C by 2 percent, so not without substantially
12:05:13 21 increasing LDL-C compared to placebo control.

12:05:17 22 So this element will also be met based on the data
12:05:21 23 in table 2 and in the paragraphs below, the paragraph below
12:05:27 24 table 2, which re-emphasizes all of those findings.

12:05:30 25 Q So just to be clear, the data you just recited is from

12:05:33 1 table 2 in the clinical study section of the Vascepa label
12:05:37 2 that we've looked at a couple times today?

12:05:40 3 A Yes, and then two sentences below the table that
12:05:42 4 reemphasized these exact findings.

12:05:45 5 Q Do you prescribe Vascepa with the intent to achieve in
12:05:49 6 your STG patient the effects recited in claim 1 of the '677
12:05:56 7 patent?

12:05:56 8 A Yes.

12:05:56 9 Q To the best of your knowledge, do other clinicians
12:06:00 10 prescribe with the attempt to achieve those lipid effects?

12:06:05 11 A Yes.

12:06:05 12 Q Do patients that you treat actually exhibit lipid effects
12:06:09 13 in line with what's recited in table 2?

12:06:11 14 A Yes.

12:06:12 15 Q And with what's recited in claim 1 of the '677 Patent?

12:06:15 16 A Yes.

12:06:16 17 Q In your opinion, will the labeling encourage clinicians
12:06:19 18 to follow each step in the method claimed in claim 1 of the
12:06:25 19 '652 patent?

12:06:26 20 A Of the '677 Patent?

12:06:28 21 Q That's what I meant, yes, I'm sorry.

12:06:30 22 A Yes.

12:06:31 23 MR. M. KENNEDY: So, Mr. Brooks, let's go to
12:06:34 24 PDX 2-38.

12:06:34 25

12:06:34 1 BY MR. M. KENNEDY:

12:06:37 2 Q And this is the other asserted claim of the '677 Patent,
12:06:41 3 and what are you attempting to show in the notation "(See
12:06:46 4 Claim 1)"?

12:06:47 5 A So, again, based on all of the previous descriptions that
12:06:51 6 we've already given and the elements that we've already
12:06:54 7 addressed, that those elements will be met by the previous
12:07:00 8 claim 1 of the '677 Patent.

12:07:03 9 Q Have you formed any opinions concerning whether the
12:07:07 10 Vascepa label encourages clinicians to prescribe Vascepa to a
12:07:11 11 subject to effect a reduction in apolipoprotein B compared to
12:07:19 12 placebo control as required by claim 8 of the '677 patent?

12:07:19 13 A Yes.

12:07:20 14 Q What is that opinion?

12:07:22 15 A That physicians who are reading the label will be
12:07:25 16 encouraged to reduce apo B. It occurred in the clinical trial
12:07:30 17 section, it's reemphasized in the paragraph below the clinical
12:07:35 18 trial section, that compared to placebo control, Vascepa will
12:07:42 19 effect a reduction in apolipoprotein B.

12:07:45 20 Q What was the magnitude of the reduction compared to
12:07:48 21 placebo control in apo B recited in the label?

12:07:52 22 A Minus 9 percent, and that was statistically significant.

12:07:57 23 Q Dr. Budoff, do clinicians prescribe Vascepa with the
12:08:01 24 intent to achieve the apo B reductions compared to placebo
12:08:06 25 control reflected in claim 8 of the '677 Patent?

12:08:09 1 A Yes.

12:08:10 2 Q In your experience, does the data show that patients
12:08:13 3 experience those effects?

12:08:15 4 A Yes, and we have ample experience that this occurs in
12:08:21 5 clinical practice.

12:08:23 6 Q So will the labeling -- the Vascepa labeling encourage
12:08:28 7 clinicians to follow each step claimed in claim 8 of the '677
12:08:32 8 Patent?

12:08:32 9 A Yes.

12:08:34 10 MR. M. KENNEDY: Let's go to PX 22.

12:08:34 11 BY MR. M. KENNEDY:

12:08:41 12 Q Dr. Budoff, do you recognize that document?

12:08:43 13 A Yes, it is U.S. patent 8,318,715.

12:08:48 14 Q Is this one of the patents you've analyzed in this case?

12:08:51 15 A Yes.

12:08:52 16 MR. M. KENNEDY: And this is on the pre-admitted
12:08:54 17 exhibit list?

12:08:56 18 THE COURT: Yes. It's Exhibit 40?

12:09:02 19 MR. M. KENNEDY: Twenty-two.

12:09:03 20 THE COURT: Is this the '715 patent?

12:09:06 21 MR. M. KENNEDY: Yeah, I have PX 22.

12:09:08 22 THE COURT: On the stipulated exhibit list --
12:09:10 23 oh, sorry, I'm looking at the file history. You're incorrect.

12:09:10 24 BY MR. M. KENNEDY:

12:09:16 25 Q Do you understand that Amarin is asserting claim 14 from

1 the '715 Patent?

2 A Yes.

3 MR. M. KENNEDY: And, Mr. Brooks, let's have
4 PDX 2-40.

5 BY MR. M. KENNEDY:

6 Q And could you just describe what the notations on the
7 right-hand side mean of this slide, PDX 2-40?

8 A And, again, for the same reasons that we've already
9 discussed, the language is exactly the same or similar to
10 those elements that we've already discussed in the claim 1 of
11 the '728 Patent, so for the same reasons the elements will be
12 met for claim 14 of the '715 patent.

13 Q Have you formed any opinions concerning whether the
14 Vascepa label encourages clinicians prescribe Vascepa to
15 effect a statistically significant reduction in triglycerides
16 and apo B without effecting a statistically significant
17 increase of LDL-C in the subject as required by claim 14 of
18 the '715 patent?

19 A Yes.

20 Q And what is that opinion?

21 A That based on a lot of the discussion we've already had,
22 that they will be encouraged to have these effects occur when
23 they use -- when they follow the label for Vascepa or its
24 generic proposed alternatives.

25 Q And, Dr. Budoff, do you understand the Court has

1 previously construed the term "without it effecting a
2 statistically significant increase in LDL-C"?

3 A Yes.

4 MR. M. KENNEDY: And I think we've touched on
5 this before, but, Mr. Brooks, if you could quickly pull up
6 PDX 2-20.

7 BY MR. M. KENNEDY:

8 Q And directing you to the bottom claim term and
9 construction, is this the construction of "without affecting a
10 statistically significant increase in LDL-C" that you applied
11 in forming your opinions?

12 A Yes.

13 MR. M. KENNEDY: Mr. Brooks if you could pull up
14 PDX 2-40 again and put it alongside trial Exhibit 1186,
15 page 2, the dosage and administration section.

16 BY MR. M. KENNEDY:

17 Q And directing your attention to 2.1, where the label
18 instructs to assess lipid levels before initiating therapy, is
19 this relevant to your opinions concerning the claim elements
20 in claim 14 of the '715 Patent?

21 A Yes.

22 Q How so?

23 A We've already discussed this, but, again, it's not just
24 telling you to assess triglyceride levels, it's telling you to
25 assess the lipid panel before initiating therapy because

changes may occur in the lipid panel.

Q And if we could go to the clinical study section, and I -- you know, obviously we've looked at this a few times, but let me start with the claim language in this claim "in the subject."

Where in the clinical study section does the Vascepa label address levels in the subject?

A Again, that's in the baseline category that we discussed earlier under the word Vascepa.

Q And does the clinical study section reflect a statistically significant reduction in TGs and apo B compared to baseline?

A Yes.

Q How do you know it's a statistically significant reduction?

A The P values are listed there. You see the asterisks. P value for a single asterisk, which is the minus 33 percent for triglycerides, the P value is minus .001, and for the apo B, the double asterisk, minus 9 percent reflects a P value of .05. Both of those are considered statistically significant.

Q And does the clinical study section disclose an increase, statistically significant or otherwise, in LDL-C levels of the subject, or in the subject?

A No, LDL-C goes down by 2 percent or by 5 percent from baseline. Both of those are decreases. So a decrease is not

1 a statistically significant increase by definition.

2 Q And, to the best of your knowledge, do clinicians
3 prescribe Vascepa with the intent to achieve the lipid effects
4 and avoidance of the lipid effects recited in claim 14 of the
5 '715 patent?

6 A Yes.

7 Q In your own experience, do your severely
8 hypertriglyceridemic patients actually achieve effects of the
9 type recited in claim 14 of the '715 patent?

10 A Yes.

11 Q And what is your expectation when you administer Vascepa
12 to a severely hypertriglyceridemic patient in terms of the
13 lipid effects those patients will experience?

14 A That the average patient, majority of my patients will
15 achieve these lipid effects when I prescribe Vascepa.

16 Q So will the Vascepa labeling encourage clinicians to
17 follow each step in the method claimed in claim 14 of the '715
18 Patent?

19 A Yes, for all the reasons that we've discussed.

20 Q Let's go to PX 30. And, Dr. Budoff, do you recognize
21 this document?

22 A Yes. This is U.S. patent 8,431,560.

23 Q And is this one of the patents you analyzed in forming
24 your opinions in this case?

25 A Yes.

12:14:55 1 MR. M. KENNEDY: Your Honor, plaintiffs
12:14:57 2 Exhibit 30 is on the preadmitted list.

12:14:58 3 THE COURT: Yes.

12:14:58 4 BY MR. M. KENNEDY:

12:14:59 5 Q Have you been informed that Amarin is asserting
12:15:02 6 infringement of claims 4 and 17 from the '560 Patent?

12:15:06 7 A Yes.

12:15:06 8 MR. M. KENNEDY: And, Mr. Brooks, if we could
12:15:08 9 have PDX 2-42.

12:15:08 10 BY MR. M. KENNEDY:

12:15:12 11 Q And, again, what does the notations in the Element Met
12:15:17 12 column mean?

12:15:18 13 A So, again, just to reiterate, these are all -- all these
12:15:22 14 elements have already been met based on our analysis of claim
12:15:26 15 1 of the '728 Patent.

12:15:28 16 Q Have you formed any opinions concerning whether the
12:15:31 17 Vascepa label encourages clinicians to prescribe Vascepa to
12:15:35 18 patients with severe hypertriglyceridemia wherein the
12:15:39 19 administering effects a reduction in fasting triglycerides of
12:15:42 20 at least about 10 percent without increasing LDL-C by more
12:15:47 21 than 5 percent in the subject?

12:15:48 22 A Yes.

12:15:49 23 Q And what is that opinion?

12:15:50 24 A As we've discussed already, the effects in the subject,
12:15:55 25 the triglyceride reductions, will be fasting triglyceride

1 reductions, which is how the trials are done and how the
2 methods are done, in practice, the fasting triglyceride levels
3 will drop by 27 percent. So that's at least 10 percent.

4 LDL-C will go down by 5 percent in the subject,
5 which is not a 5 percent increase, but rather a 5 percent
6 decrease.

7 So all three of these elements will be met when
8 physicians follow the label.

9 Q And, again, these are -- you're referring to the data in
10 the clinical study section of the Vascepa label that we've
11 looked at?

12 A Yes.

13 Q When you administer Vascepa to a severely
14 hypertriglyceridemic patient, do you expect to achieve results
15 of the type claimed by claim 4 of the '560 patent?

16 A Yes.

17 Q When you administer Vascepa to a patient, do you achieve
18 effects of the type claimed by claim 4 of the '560 Patent?

19 A Yes.

20 Q To the best of your knowledge, do clinicians prescribe
21 with the intent to achieve the results -- the lipid effects --
22 the results of lipid effects claimed by claim 4 of the '560
23 patent?

24 A Yes.

25 Q So will the labeling encourage clinicians to follow each

12:17:14 1 step in the method claimed in claim 4 of the '560 patent?

12:17:18 2 A Yes.

12:17:18 3 MR. M. KENNEDY: Okay. Then let's please look
12:17:20 4 at PDX 244.

12:17:20 5 BY MR. M. KENNEDY:

12:17:26 6 Q And, again, is this asserted claim 17 of the '560 patent?

12:17:31 7 A Yes.

12:17:32 8 Q And what are you denoting with the notations in the
12:17:36 9 Element Met column?

12:17:39 10 A Similar to the last few claims, again, these are the same
12:17:44 11 language that was used and elements that were met based on the
12:17:48 12 same analysis for claim 1 of the '728 Patent.

12:17:53 13 Q Have you formed any opinions concerning whether the
12:17:56 14 Vascepa label encourages clinicians to prescribe Vascepa and
12:18:01 15 expect to achieve effecting a reduction in fasting
12:18:06 16 triglycerides of at least about 20 percent without increasing
12:18:10 17 LDL-C in the subject compared to placebo control as required
12:18:14 18 by claim 17 of the '560 Patent?

12:18:16 19 A Yes.

12:18:17 20 Q What is that opinion?

12:18:18 21 A That physicians following the label will see more than a
12:18:25 22 20 percent drop in fasting triglycerides, it dropped by
12:18:30 23 33 percent compared to control.

12:18:32 24 So that element will be met when they follow the
12:18:35 25 label and look at the clinical trials section, they will see

12:18:38 1 that there is no increase in LDL-C compared to placebo
12:18:42 2 control. So all of these elements will be met as physicians
12:18:46 3 follow the label.

12:18:47 4 Q Dr. Budoff, do you administer Vascepa with the intent to
12:18:50 5 effect reductions in fasting triglycerides of about 20 percent
12:18:54 6 without increasing LDL-C in the subject compared to placebo
12:18:59 7 control as required by claim 17 of the '560 patent?

12:19:02 8 A Yes.

12:19:02 9 Q When you administer Vascepa to patients with STG, do they
12:19:09 10 achieve results in line with those required by claim 17 of the
12:19:13 11 '560 patent?

12:19:14 12 A Yes.

12:19:15 13 Q Do other physicians prescribe Vascepa with the intent to
12:19:19 14 achieve the lipid results claimed in claim 17 of the '560
12:19:23 15 patent?

12:19:24 16 A Yes.

12:19:25 17 Q So, in your opinion, will the Vascepa labeling encourage
12:19:28 18 clinicians to follow each step in the method claimed by claim
12:19:33 19 17 of the '560 patent?

12:19:34 20 A Yes.

12:19:35 21 Q And then let's go to the PX 31, and this is -- Dr.
12:19:47 22 Budoff, do you recognize this document?

12:19:49 23 A Yes, this is U.S. patent 8,518,929.

12:19:52 24 Q And is this one the patents you analyzed in forming your
12:19:56 25 opinions in this case?

12:19:57 1 A Yes.

12:19:58 2 Q You understand that Amarin is asserting claims 1 and 5
12:20:02 3 from this patent?

12:20:03 4 A Yes.

12:20:04 5 MR. M. KENNEDY: And, Mr. Brooks, can we go to
12:20:06 6 slide PDX 2-46.

12:20:06 7 BY MR. M. KENNEDY:

12:20:11 8 Q And, Dr. Budoff, what have you shown on this slide?

12:20:14 9 A So, again, as previously stated, all of the elements will
12:20:19 10 be met using the same analysis as claim 1 of the '728 Patent.

12:20:24 11 Q Does the Vascepa label instruct daily administration of
12:20:29 12 Vascepa?

12:20:30 13 A Yes.

12:20:31 14 Q Daily administration of 4 grams of a pharmaceutical
12:20:37 15 composition?

12:20:38 16 A Yes.

12:20:39 17 Q And will the labeling -- will the Vascepa labeling
12:20:45 18 encourage clinicians to follow each step in the method of
12:20:49 19 claim 1 of the '929 patent?

12:20:51 20 A Yes.

12:20:51 21 Q And then slide 2-47, this is claim -- asserted claim 5 of
12:20:59 22 the '929 patent.

12:21:01 23 And, again, Dr. Budoff, can you just very briefly
12:21:05 24 explain what this slide shows.

12:21:06 25 A Yes. So, again, the elements we just discussed in claim

1 are met by the analysis of claim 1 on the previous slide, and now there's two new elements here, "effective to reduce apolipoprotein B in subjects."

Q Have you formed any opinions concerning whether the Vascepa label encourages clinicians to administer Vascepa to patients with severe hypertriglyceridemia effective to reduce apolipoprotein B in subjects?

A Yes.

Q And what is that opinion?

A That the apolipoprotein B goes down in subjects as seen in table 2 of the label, and physicians will be encouraged to use Vascepa to reduce apolipoprotein B in their subjects.

MR. M. KENNEDY: And since we haven't looked at apolipoprotein B quite as much today, Mr. Brooks, can we pull up table 2 alongside this slide.

BY MR. M. KENNEDY:

Q And, Dr. Budoff, does table 2, the clinical study section of the Vascepa label, support your opinion that the label will encourage clinicians to administer Vascepa to reduce apolipoprotein B in subjects?

A Yes, you can see that. Compared to baseline there was a minus 4 percent reduction in apo B, and the overall difference compared to placebo control is minus 9 percent, and it's called out again in the sentence below the table, Vascepa 4 grams per day reduced median TG, VLDL-C, and apo B levels from

12:22:58 1 baseline relative to placebo.

12:23:01 2 Q Dr. Budoff, do you prescribe Vascepa with the intent to
12:23:04 3 reduce apolipoprotein B?

12:23:07 4 A Yes.

12:23:08 5 Q When you prescribe Vascepa, do you observe reductions in
12:23:14 6 apolipoprotein B in your patients?

12:23:18 7 A Yes.

12:23:18 8 Q To your knowledge, do other clinicians prescribe Vascepa
12:23:20 9 with the intent to reduce apolipoprotein B in the expectation
12:23:22 10 that those reductions will be achieved?

12:23:24 11 A Yes.

12:23:25 12 Q So will the Vascepa labeling encourage clinicians to
12:23:30 13 follow each step in the method claimed by claim 5 of the '929
12:23:35 14 patent?

12:23:35 15 A Yes.

12:23:36 16 Q And as with all the other Vascepa label related
12:23:39 17 questions, if I ask you with respect to the Hikma and DRL
12:23:43 18 labels, would your answer be the same?

12:23:45 19 A Yes.

12:23:50 20 MR. M. KENNEDY: So I have no further questions
12:23:51 21 for the witness at this time.

12:23:52 22 THE COURT: Thank you, Mr. Kennedy.

12:23:58 23 MR KLEIN: Your Honor, do you want to break or
12:24:00 24 keep going?

12:24:01 25 THE COURT: Well, if I had my preference, we

12:24:04 1 would keep going, but I think we should take a lunch break at
12:24:07 2 this time, so let's take a 30-minute lunch break. Thank you.

3 (The noon recess was taken.)

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01:04:47 3
01:04:47 4 THE COURT: Please be seated.

01:04:48 5 Mr. Klein?

01:04:52 6 MR KLEIN: Thank you, Your Honor.

01:04:54 7 Good afternoon, Dr. Budoff.

01:04:54 8 THE WITNESS: Afternoon.

01:04:56 9 MR. KLEIN: We obviously met at your deposition,
01:04:58 10 but, for the record, I'm Charles Klein, and I will be asking
01:05:02 11 you some questions on behalf of the defendants.

01:04:53 12 CROSS-EXAMINATION

01:04:53 13 BY MR. KLEIN:

01:05:05 14 Q Each asserted patent in this case requires using
01:05:11 15 icosapent for at least 12 weeks. You understand that, right?

01:05:13 16 A Yes.

01:05:13 17 Q Okay. And defendants' product labels do not specifically
01:05:21 18 encourage using icosapent for at least 12 weeks, correct?

01:05:24 19 A No, they do.

01:05:25 20 Q They specifically encourage using icosapent for at least
01:05:30 21 12 weeks?

01:05:31 22 A Yes.

01:05:32 23 Q Okay. Let's take a look at the indication. And for the
01:05:38 24 record, you recognize the top snapshot as DX 2248? That's the
01:05:44 25 Vascepa MARINE indication?

01:05:46 1 A Yes.

01:05:47 2 Q Okay. And we're not going to talk about -- you
01:05:49 3 understand there's a new indication, right?

01:05:51 4 A Yes.

01:05:52 5 Q Okay. We're not going to talk about that other
01:05:54 6 indication today so if I refer simply to the Vascepa
01:05:58 7 indication, can we understand that we're talking about the
01:06:01 8 MARINE indication?

01:06:02 9 A Yes.

01:06:02 10 Q Okay. And then we have the Hikma indication, which is
01:06:06 11 DX 2256, and the DRL indication which is DX 2266, and I
01:06:13 12 believe on direct you testified that these three indications
01:06:17 13 are materially identical, correct?

01:06:22 14 A Yes.

01:06:22 15 Q All right. Neither the Vascepa indication nor
01:06:28 16 defendants' indications is actually telling doctors to use the
01:06:34 17 drug for at least 12 weeks, right?

01:06:36 18 A It does not state 12 weeks, that's correct.

01:06:39 19 Q Right. Right. And if we look at the dosage and
01:06:42 20 administration section, and here I've got the Hikma label,
01:06:48 21 DX 2256, on the screen, but do you understand that the DRL
01:06:52 22 label is materially identical?

01:06:54 23 A Yes.

01:06:55 24 Q Okay. And the dosage and administration section in
01:07:02 25 defendants' labels doesn't specify any duration of treatment,

01:07:07 1 correct?

01:07:07 2 A Correct.

01:07:08 3 Q And so defendants' dosage and administration section
01:07:12 4 doesn't specifically encourage using icosapent for at least
01:07:18 5 12 weeks, right?

01:07:19 6 A Correct.

01:07:20 7 Q In fact, there's no explicit instruction in the Vascepa
01:07:23 8 label or in defendants' labels to use icosapent for at least
01:07:28 9 12 weeks, right?

01:07:28 10 A No, there is explicit language.

01:07:31 11 Q There -- listen carefully to the question, please.

01:07:33 12 Is there -- there is no explicit instruction
01:07:37 13 anywhere in the Vascepa label or in defendants' labels telling
01:07:42 14 doctors to use icosapent for at least 12 weeks.

01:07:45 15 A There is explicit language in the Hikma and DRL labels
01:07:51 16 instructing physicians to use Vascepa or icosapent ethyl for
01:07:58 17 12 weeks.

01:07:58 18 Q So what language are you referring to?

01:08:00 19 A The clinical trials section.

01:08:02 20 Q Okay. We'll get to that later, but the clinical trials
01:08:06 21 section is describing a 12-week study, the MARINE study,
01:08:10 22 right?

01:08:10 23 A Well, I was just trying to answer your question.

01:08:13 24 My understanding of the infringement is the label
01:08:15 25 taken in its entirety. So when you ask me does the label

01:08:20 1 state 12 weeks, and I say yes, I believe I'm correct.

01:08:23 2 Q And we'll get to the clinical trial section later in the
01:08:27 3 examination, but just to make sure we're on the same page, the
01:08:30 4 clinical trial section of defendants' labels does not say,
01:08:34 5 doctors, you should give the drug for at least 12 weeks. Can
01:08:37 6 we agree on that?

01:08:38 7 A It does not say those words, that's correct.

01:08:41 8 Q And instead, the Vascepa label, as well as defendants'
01:08:45 9 labels, leave it entirely up to the physician's discretion to
01:08:50 10 determine the duration of treatment, correct?

01:08:52 11 A Yes.

01:08:54 12 Q Now, so, what that means is defendants' labels will allow
01:09:02 13 doctors to tailor treatment duration to the individual
01:09:06 14 patients, correct?

01:09:07 15 A Yes, but they have to be concordant with the disease
01:09:12 16 that's indicated.

01:09:13 17 Q Right. Of course. But doctors can follow defendants'
01:09:16 18 labels and prescribe icosapent indefinitely if they want.
01:09:22 19 That's your opinion, right?

01:09:23 20 A Yes.

01:09:23 21 Q But a doctor could also prescribe icosapent for only ten
01:09:27 22 weeks, if that's what's called for, for the particular patient
01:09:30 23 and the patient concerns, correct?

01:09:32 24 A I can't imagine that scenario, but if that scenario
01:09:37 25 existed, then yes, I agree.

01:09:39 1 Q Okay. Then we'll come back to that.

01:09:41 2 Either way, the labeling gives this decision, the
01:09:45 3 treatment duration, to the doctor to make, right?

01:09:47 4 A Yes.

01:09:47 5 Q And so it would be entirely consistent with defendants'
01:10:03 6 labels for a doctor to prescribe icosapent for less than
01:10:08 7 12 weeks, right?

01:10:09 8 A Yes.

01:10:11 9 Q Now, we talked about how there's no explicit instruction
01:10:21 10 in the labels that actually tells doctors you should use
01:10:27 11 icosapent for at least 12 weeks. Do you remember that?

01:10:29 12 A Yes. I believe I feel there is explicit language, and
01:10:34 13 you feel there is not. But, yes, I remember that previous
01:10:36 14 discussion we just had.

01:10:38 15 Q Okay. But I think you said there's no explicit language
01:10:41 16 that actually tells doctors you should use this product for at
01:10:45 17 least 12 weeks, correct?

01:10:46 18 A Your quote is not in the label, I agree with that.

01:10:49 19 Q Right. You're referring to the 12 weeks term in the
01:10:52 20 clinical studies section, right?

01:10:54 21 A Yes, which I believe instructs physicians to use it for
01:10:57 22 12 weeks.

01:10:58 23 Q Okay. So your opinion really is, when doctors read the
01:11:01 24 label as a whole, including the 12 weeks statement in the
01:11:05 25 clinical studies section, that will apply to doctors that they

01:11:09 1 should go ahead and use the drug for at least 12 weeks, right?

01:11:12 2 A Yes.

01:11:13 3 Q On the screen is DX 2256 and, for the record, it's
01:11:24 4 DDX 3.3. This is -- you recognize this as the indications and
01:11:28 5 usage section of Hikma's proposed label, right?

01:11:31 6 A Yes.

01:11:31 7 Q And, obviously, as -- the indication is for severe
01:11:36 8 hypertriglyceridemia, right?

01:11:37 9 A Yes.

01:11:38 10 Q And your opinion is that doctors know that this is a
01:11:41 11 chronic condition?

01:11:42 12 A Yes.

01:11:43 13 Q Okay. And your opinion is that the condition, severe
01:11:48 14 hypertriglyceridemia, requires indefinite drug therapy, right?

01:11:52 15 A Yes.

01:11:53 16 Q Okay. I want to make sure I understand what you're
01:11:55 17 saying. Are you saying that doctors will read defendants'
01:11:59 18 indication as necessarily, in all circumstances, requiring
01:12:05 19 indefinite treatment?

01:12:07 20 A No.

01:12:09 21 Q And why do you say no?

01:12:11 22 A Well, not everybody can tolerate therapy forever so we
01:12:16 23 never use absolutes, but I would say doctors will read this
01:12:20 24 label and say, oh, severe hypertriglyceridemia, that's a
01:12:25 25 chronic condition, I'm going to treat this chronically.

01:12:29 1 To say that in every case they use it indefinitely
01:12:33 2 is, obviously, not possible. Some patients don't tolerate
01:12:37 3 therapy, some patients can't get therapy, so we can't use
01:12:41 4 absolutes when we talk about what a person of ordinary skill
01:12:45 5 in the art will do in a given situation.

01:12:48 6 Q Okay. And we'll come back to that concept.

01:12:51 7 I want to direct you to paragraph 357 of plaintiffs'
01:12:58 8 proposed findings of fact, and this is ECF number 331.

01:13:03 9 You probably haven't seen this, but I will represent
01:13:06 10 to you that this is a statement from plaintiffs' to the Court
01:13:09 11 last week, and in this proposed findings of fact, plaintiffs
01:13:15 12 propose that the Court find that clinicians will read
01:13:19 13 defendants' labeling with the understanding that severe
01:13:21 14 hypertriglyceridemia is almost invariably a chronic condition.

01:13:26 15 Do you see that?

01:13:27 16 A Yes.

01:13:27 17 Q And as a matter of linguistics, almost invariably isn't
01:13:34 18 always, right?

01:13:34 19 A Correct.

01:13:35 20 Q Okay. And so is this consistent with your testimony that
01:13:44 21 it's almost invariably a chronic condition?

01:13:47 22 A Yes.

01:13:48 23 Q Okay. And so you're not testifying that severe
01:20:37 24 hypertriglyceridemia is always a chronic condition, correct?

01:20:37 25 A Correct.

01:20:37 1 Q And do you understand that defendants' labels never
01:20:37 2 actually say that severe hypertriglyceridemia is a chronic
01:20:37 3 condition, right?

01:20:37 4 A Yes. I think Dr. Ketchum went through that yesterday.

01:20:37 5 Q Yeah, I was just going to bring that up. You were here,
01:20:37 6 right?

01:20:37 7 A Yes.

01:20:37 8 Q And you understood that there was a proposal to the FDA
01:20:37 9 from Amarin to characterize the Vascepa patient population as
01:20:37 10 requiring chronic care, but FDA rejected that, right?

01:20:37 11 A Yes.

01:20:37 12 Q But your opinion is that a doctor would see the
01:20:37 13 indication and understand that severe hypertriglyceridemia is
01:20:37 14 very often a chronic condition, right?

01:20:37 15 A Yes.

01:20:37 16 Q Okay. And so what you're really saying is that a doctor
01:20:37 17 knows that severe hypertriglyceridemia can be a chronic
01:20:37 18 condition, not that it always is a chronic condition, right?

01:20:38 19 A I think we keep changing the adjectives, but why don't we
01:20:38 20 stick with almost invariably just to be concise because we've
01:20:38 21 gone from almost invariably now to can.

01:20:38 22 Q Okay.

01:20:38 23 A Which I think is a pretty broad change in terminology.
01:20:38 24 So I'll stick with this language as language that I'm
01:20:38 25 comfortable with.

01:20:38 1 Q Okay. Well, you agree it's not always a chronic
01:20:38 2 condition, right?

01:20:38 3 A That's correct.

01:20:38 4 Q So just as a matter of logic, what you're saying is it
01:20:38 5 can be. Now, in your view, it is almost invariably, but
01:20:38 6 you're really saying it can be a chronic condition, correct?

01:20:38 7 A It is a chronic condition in almost all cases, but not
01:20:38 8 all cases.

01:20:38 9 I described the reversible causes earlier, diabetes
01:20:38 10 out of control, binge drinking, hypothyroidism, as other
01:20:38 11 causes that can push people up into the severe
01:20:38 12 hypertriglyceridemic range that would not be considered a
01:20:38 13 chronic condition.

01:20:38 14 Q Okay. Thanks. You're getting to my next point.

01:20:38 15 So you were here for opening statements as well,
01:20:38 16 right?

01:20:38 17 A Yes.

01:20:38 18 Q And did you see this testimony from Dr. Toth during the
01:20:38 19 opening statements?

01:20:38 20 A Yes.

01:20:38 21 Q And you know who Dr. Toth is, right?

01:20:38 22 A Yes.

01:20:38 23 Q You understand he's one of Amarin's experts in this case.

01:20:38 24 A Yes, I know Dr. Toth.

01:20:38 25 Q Yeah, you actually know him otherwise as --

01:20:38 1 A Yes, we are -- we are on different guidelines and
01:20:39 2 committees together.

01:20:39 3 Q And so you saw that Dr. Toth testified in his deposition
01:20:39 4 that there would be circumstances where very high
01:20:39 5 triglycerides was an acute phenomenon, right?

01:20:39 6 A Yes.

01:20:39 7 Q And you agree with that?

01:20:39 8 A Yes, for the reasons I've already stated.

01:20:39 9 Q Right. And that's what you meant by the reversible
01:20:39 10 causes?

01:20:39 11 A Yes.

01:20:39 12 Q Okay. And doctors would know from reading defendants'
01:20:39 13 indications that sometimes severe hypertriglyceridemia can be
01:20:39 14 an acute phenomenon, right?

01:20:39 15 A Yes.

01:20:39 16 Q Did you also see this testimony from Dr. Peck?

01:20:39 17 A Yes.

01:20:39 18 Q Do you know Dr. Peck?

01:20:39 19 A No, not outside of this context.

01:20:39 20 Q Okay. But you understand that Dr. Peck is Amarin's
01:20:39 21 regulatory expert in this case?

01:20:39 22 A Yes.

01:20:39 23 Q And so you saw that Dr. Peck said he doesn't think that
01:20:39 24 the indicated use of Vascepa is limited to chronic use, right?

01:20:39 25 A Yes.

01:20:39 1 Q Okay. And you're not an expert in FDA regulations,
01:20:39 2 correct?

01:20:39 3 A Correct.

01:20:39 4 Q So you agree with Dr. Peck's testimony when he says, "I
01:20:39 5 don't think the indicated use of Vascepa is limited to chronic
01:20:39 6 use." Correct?

01:20:39 7 A I disagree with that.

01:20:39 8 Q You disagree with what -- so you think Dr. Peck is not
01:20:39 9 accurately characterizing the indication from an FDA
01:20:39 10 regulatory perspective?

01:20:39 11 A I didn't have a chance to discuss with Dr. Peck. It
01:20:39 12 would be -- I don't know, I think you guys throw around the
01:20:40 13 word hearsay -- for me to take this at face value without any
01:20:40 14 context.

01:20:40 15 But I believe, if you're asking my opinion, that the
01:20:40 16 current indicated use of Vascepa, you're supposed to
01:20:40 17 systematically eliminate all of the acute causes, that's
01:20:40 18 clearly listed in the label, and then the resultant treatment,
01:20:40 19 the resulted indication for Vascepa is, after you've removed
01:20:40 20 all of the acute indications, you use Vascepa which would
01:20:40 21 leave only chronic use.

01:20:40 22 So my reading of the label -- and I'm not arguing
01:20:40 23 with Dr. Peck, but my reading of the label is that the current
01:20:40 24 indicated use of Vascepa is for the resultant people who have
01:20:40 25 genetic problems, and thus it is a chronic condition.

01:20:40 1 Q Okay.

01:20:40 2 A So it's only indicated to -- for chronic use.

01:20:40 3 Q And we'll unpack that a bit.

01:20:40 4 But what I'm getting at here is you're offering that
01:20:40 5 opinion from the perspective of a physician who will apply the
01:20:40 6 label, correct?

01:20:40 7 A Yes.

01:20:40 8 Q Okay. And do you understand that Dr. Peck is offering an
01:20:40 9 opinion from the perspective of what FDA approved?

01:20:41 10 A Yes. Again, I wasn't there. I didn't read Dr. Peck's
01:20:41 11 full deposition transcript. I see it referenced here, so I
01:20:41 12 really don't think I can speak to this one sentence.

01:20:41 13 But my opinion is I agree with Dr. Peck on this one
01:20:41 14 question. I would answer it differently.

01:20:41 15 Q Okay. But you are not an FDA regulatory expert, right?

01:20:41 16 A That's been established.

01:20:41 17 Q And you're not expert in FDA labeling, right?

01:20:41 18 A That's been established.

01:20:41 19 Q So if Dr. Peck testifies from the FDA perspective that
01:20:41 20 FDA did not limit the indication to chronic use, you would
01:20:41 21 have no basis to dispute that, correct?

01:20:41 22 A I would not argue with Dr. Peck on the FDA, but I believe
01:20:41 23 we already heard about the FDA, and it said should it be used
01:20:41 24 for acute use, and the answer was not applicable.

01:20:41 25 So, again, my reading from yesterday, and my

1 understanding of what the FDA already opined on, is that it's
2 not appropriate for acute use because they said not
3 applicable. That was in the questions in the FDA documents
4 that were presented yesterday.

5 But, again, I'm not going to get into an FDA
6 argument with Dr. Peck.

7 Q And just to be clear, you're referring to the form that
8 was used in Dr. Ketchum's testimony?

9 A Yes.

10 Q You did not offer any opinions on that form in your
11 report, correct?

12 A No.

13 Q And you're not offering any opinions on that form today,
14 correct?

15 A I'm only trying to answer your question as best I can.

16 Q Okay. But -- so you say you disagree with Dr. Peck at
17 least from a physician perspective, but you do agree it would
18 be consistent with the Vascepa labeling for a doctor to
19 prescribe Vascepa for fewer than 12 weeks, correct?

20 A Yes.

21 Q Let's go back to the indication, and, again, I'm using
22 Hikma's indication for simplicity, but you understand DRL's
23 indication is the same, right?

24 A Yes.

25 Q And we talked about this a moment ago.

01:20:54 1 You are relying on the term severe
01:20:57 2 hypertriglyceridemia in the indication as signaling to doctors
01:21:02 3 that they should use the drug long-term, correct?

01:21:05 4 A Yes.

01:21:08 5 Q Okay. Now, let's focus on that term.

01:21:10 6 The term severe hypertriglyceridemia has a
01:21:13 7 well-known meaning to doctors who treat the condition, right?

01:21:16 8 A Yes.

01:21:16 9 Q And the meaning of severe hypertriglyceridemia is
01:21:19 10 actually in the indication. It means greater than or equal to
01:21:25 11 500 milligrams per deciliter, right?

01:21:26 12 A Yes.

01:21:27 13 Q And that's it. That's -- that's the definition of severe
01:21:31 14 hypertriglyceridemia, right?

01:21:32 15 A Well, no. I mean, there's definitions of diseases. This
01:21:37 16 is not a definition. This is just stating the term, severe
01:21:41 17 hypertriglyceridemia.

01:21:41 18 But, yes, it's characterized by triglycerides
01:21:46 19 greater than 500 milligrams per deciliter in the blood in the
01:21:49 20 fasting state. But, yes, that's -- that's what I construe to
01:21:54 21 be severe hypertriglyceridemia.

01:21:57 22 Q Right. And that is how doctors diagnose severe
01:22:01 23 hypertriglyceridemia. They have a blood test taken, and if
01:22:04 24 the triglycerides are above 500, then the doctors conclude the
01:22:08 25 patient has severe hypertriglyceridemia, right?

01:22:11 1 A Yes.

01:22:14 2 Q Okay. And severe hypertriglyceridemia has various
01:22:17 3 causes, right?

01:22:18 4 A Yes.

01:22:19 5 Q And the diagnosis of severe hypertriglyceridemia does not
01:22:25 6 turn on the cause, right?

01:22:27 7 A That's correct.

01:22:28 8 Q So as long as the patients have triglyceride levels above
01:22:33 9 500, regardless of why, they have severe hypertriglyceridemia.

01:22:38 10 A Just to be concise, I would say fasting triglycerides
01:22:42 11 greater than 500, that's the definition.

01:22:45 12 Q And that's a fair point. And let's just assume, when we
01:22:48 13 talk about the triglyceride levels, that we're talking about
01:22:52 14 fasting levels. I think that's a fair characterization.

01:22:55 15 And doctors know that when patients have
01:23:00 16 triglycerides above 500, the goal is to prevent an acute
01:23:06 17 pancreatitis attack, right?

01:23:08 18 A Yes.

01:23:09 19 Q Okay. And so the indication is signaling to doctors that
01:23:13 20 if the patient has triglycerides above 500, no matter the
01:23:19 21 cause, that icosapent can be used in that patient, right?

01:23:25 22 A No, that's not how I read the label. I read the label as
01:23:29 23 you must exclude acute causes, and then you would use Vascepa.
01:23:34 24 That's how I read the label, and that's how I believe
01:23:37 25 physicians read the label.

01:23:39 1 Q Okay. And you're referring to the dosage and
01:23:41 2 administration section, right?

01:23:42 3 A Yes. But when you say the label, I'm taking the label --
01:23:46 4 again, my understanding of infringement is the label taken in
01:23:49 5 its entirety.

01:23:50 6 So I don't think it would be fair to say, "Doctor,
01:23:53 7 you're only allowed to read the first line. Now what do you
01:23:56 8 want to do with your patient?"

01:23:57 9 Q Okay. No. And that's a fair point, Doctor, and we'll
01:24:00 10 get to the doseage and administration section, but for now
01:24:04 11 let's focus on the indication itself.

01:24:06 12 A doctor looking at the indication would understand
01:24:09 13 that if the patient presents with triglycerides over 500, then
01:24:13 14 icosapent can be used in that patient subject to, you know,
01:24:17 15 other instructions in the label, correct?

01:24:20 16 A Yes.

01:24:20 17 Q And a doctor would understand that if icosapent is being
01:24:27 18 used, it will be used as an adjunct to diet, right?

01:24:31 19 A Yes.

01:24:31 20 Q And the hope is that using icosapent as an adjunct to
01:24:36 21 diet will avoid pancreatitis.

01:24:39 22 A Yes.

01:24:39 23 Q All doctors who treat severe hypertriglyceridemia
01:24:43 24 understand when they read the indication of Vascepa or
01:24:48 25 defendants' labels, that that's the goal of using the drug,

01:24:51 1 right?

01:24:51 2 A That is at least the primary goal, yes.

01:24:55 3 Q Yes. Well, okay.

01:25:00 4 Let's go to the ATP III guidelines, and you talked
01:25:04 5 about this on direct, right?

01:25:06 6 A Yes.

01:25:06 7 MR. KLEIN: And, for the record, this is
01:25:10 8 DX 1526, page 28, and the document has been admitted into
01:25:14 9 evidence.

01:25:14 10 BY MR. KLEIN:

01:25:17 11 Q Now, the ATP guidelines explain that when triglycerides
01:25:21 12 are very high, greater than or equal to 500, the initial aim
01:25:26 13 of therapy is to prevent acute pancreatitis through
01:25:31 14 triglyceride lowering, and you agree with that, right?

01:25:33 15 A Yes.

01:25:34 16 Q Okay. And that's the primary treatment aim regardless of
01:25:38 17 why the patient has triglycerides above 500, right?

01:25:41 18 A Yes.

01:25:42 19 Q If we go to the next slide, which is DDX 3.9, we're on
01:25:49 20 DX 1526, page 28, the guidelines go on to say this approach --
01:25:57 21 in other words, the aim of preventing acute pancreatitis
01:26:00 22 through triglyceride lowering -- requires very low fat diets,
01:26:05 23 weight reduction, increased physical activity, and usually a
01:26:09 24 triglyceride-lowering drug, and I omitted the parentheticals,
01:26:13 25 right?

01:26:14 1 A Yes.

01:26:14 2 Q And this approach is consistent with your own practice,
01:26:19 3 right?

01:26:19 4 A Yes, except they don't stipulate -- they don't -- this is
01:26:23 5 pre-2002, this was pre-Vascepa, so the only two choices given
01:26:27 6 here are fibrate and nicotinic acid, and now we have two other
01:26:33 7 drugs that are for this indication. But, yes.

01:26:35 8 Q Okay. Yeah. Putting aside the specific drugs, this
01:26:38 9 statement in the ATP III guidelines is consistent with your
01:26:39 10 practice, right?

01:26:41 11 A Yes.

01:26:42 12 Q And to be clear, the guidelines here say the approach
01:26:46 13 focuses on diet, weight reduction, increased physical
01:26:50 14 activity, and usually a triglyceride-lowering drug, right?

01:26:54 15 A Yes.

01:26:54 16 Q Okay. And the guidelines don't tell doctors if patients
01:26:59 17 present with severe hypertriglyceridemia, you should always
01:27:04 18 use drug therapy, correct?

01:27:06 19 A That's correct.

01:27:07 20 Q And that, too, is consistent with your own practice,
01:27:10 21 right?

01:27:10 22 A Yes.

01:27:11 23 Q Okay. Let's go to the next slide, and I'm just
01:27:24 24 highlighting a different sentence on the same page.

01:27:27 25 The guidelines then say only after triglyceride

01:27:30 1 levels have been lowered to less than 500 milligrams per
01:27:35 2 deciliter should attention turn to LDL lowering to reduce risk
01:27:39 3 for CHD, right?

01:27:42 4 A Yes.

01:27:43 5 Q And, in other words, once the triglyceride -- once the
01:27:48 6 triglyceride levels in a patient dip below 500, you become
01:27:53 7 less concerned about pancreatitis and your focus turns to
01:27:58 8 cardiovascular treatment, correct?

01:27:59 9 A Yes, and I've tried to outline that today in the direct
01:28:02 10 testimony as well.

01:28:03 11 Q Okay. And I think you talked about this as well, this is
01:28:08 12 how the ATP III characterizes the different levels of
01:28:13 13 triglycerides, right?

01:28:14 14 A Yes.

01:28:15 15 Q Okay. And high triglycerides are 200 to 499, right?

01:28:21 16 A Yes.

01:28:21 17 Q Okay. And some patients are in this range, the high
01:28:26 18 triglyceride range, because of generic -- genetic factors,
01:28:31 19 correct?

01:28:32 20 A Yes.

01:28:32 21 Q And -- but even if a patient has triglycerides over 500,
01:28:38 22 and you're able to reduce the pancreatitis risk by getting the
01:28:43 23 triglycerides into the very high -- into the high triglyceride
01:28:48 24 range, you still want to get those levels lower, right?

01:28:51 25 A I think we know a lot more now also given the results of

01:28:55 1 the REDUCE-IT trial. But, yes, I think that is -- still I
01:28:58 2 would still like to get the triglycerides lower than 499.

01:29:01 3 Q You would like to get them lower than 200, right?

01:29:05 4 A Yes.

01:29:05 5 Q But that goal, that desire, is based on cardiovascular
01:29:10 6 risk, not pancreatitis risk, correct?

01:29:14 7 A That's correct.

01:29:15 8 Q And you understand that the goal with regard to severe
01:29:23 9 hypertriglyceridemia is not -- the primary goal is not to
01:29:29 10 reduce cardiovascular risk but to reduce the acute
01:29:33 11 pancreatitis risk, right?

01:29:35 12 A Yes.

01:29:35 13 Q Okay. And defendants' products are not indicated to
01:29:39 14 reduce triglycerides in patients who have baseline levels
01:29:44 15 below 500, right?

01:29:45 16 A Correct.

01:29:46 17 Q And so a doctor using Vascepa or defendants' products,
01:29:50 18 should they come to market, solely to reduce cardiovascular
01:29:56 19 risk would be using icosapent off label, again, ignoring the
01:30:01 20 new REDUCE-IT indication.

01:30:03 21 A Yes.

01:30:04 22 Q And so you understand defendants' products are not
01:30:08 23 indicated to improve cardiovascular outcomes, right?

01:30:12 24 A Correct.

01:30:14 25 Q And you also understand -- although I don't think it came

01:30:19 1 up during your direct, but you understand that defendants are
01:30:22 2 carving out this second REDUCE-IT indication from their
01:30:27 3 proposed labels, right?

01:30:29 4 A Yes.

01:30:30 5 Q Now, we talked about how there can be various causes of
01:30:38 6 very high triglycerides, right?

01:30:39 7 A Yes.

01:30:41 8 Q And most commonly severe hypertriglyceridemia is caused
01:30:45 9 by unhealthy diet and poor lifestyle choices, right?

01:30:49 10 A No, most commonly it's caused by genetics. We've
01:30:54 11 reviewed that, I think, a few times.

01:30:56 12 Q Now, when you say genetics, there are really two
01:31:00 13 different types of genetic -- genetic causes of severe
01:31:05 14 hypertriglyceridemia. For example, there are some genetic
01:31:08 15 causes that, no matter what you do with diet and exercise, you
01:31:13 16 are absolutely going to need drugs, correct?

01:31:15 17 A Yes.

01:31:16 18 Q And these patients generally have triglycerides well
01:31:25 19 above 500, right?

01:31:26 20 A The more severe the genetic abnormality, the higher the
01:31:31 21 triglyceride levels will go, yes.

01:31:33 22 Q I mean, we're talking sometime 1,000 or even 2,000,
01:31:36 23 correct?

01:31:36 24 A Yes.

01:31:37 25 Q Okay. And the -- these conditions include familial

01:31:47 1 hypertriglyceridemia; is that right?

01:31:49 2 A Yes.

01:31:49 3 Q And familial combined hyperlipidemia; is that right?

01:31:54 4 A That's usually represented by -- combined implies that
01:31:58 5 multiple di -- there's multiple problems and usually the
01:32:02 6 triglycerides are not as high and their LDL, their bad
01:32:07 7 cholesterol is also high.

01:32:08 8 So there are, again -- I mean, I listed some of
01:32:11 9 the -- I think scientific statement from the American Heart
01:32:15 10 Association talked about the seven most common genetic
01:32:18 11 abnormalities.

01:32:19 12 Q Okay. And another one is defects in lipoprotein lipase
01:32:23 13 or apo C-2, right?

01:32:25 14 A Yes.

01:32:26 15 Q Okay. But these types of genetic disorders where the
01:32:30 16 patients have triglycerides at the 1,000, 2,000 level, these
01:32:34 17 are pretty rare, right?

01:32:36 18 A Some of those specific ones are pretty rare, but some of
01:32:41 19 them are what we call incomplete transmissions.

01:32:44 20 So, for example, somebody could have a triglyceride
01:32:47 21 level 550 or 600, and if we were to do genetic testing, we
01:32:52 22 might find that they have a partial -- partial expression of
01:32:56 23 that problem.

01:32:57 24 In other words, they don't have to be pure -- kind
01:32:59 25 of like not be purebreds per se in the regard to that

01:33:04 1 disorder. But the patients who have pure genetic disorders,
01:33:10 2 they tend to have very high triglycerides as you're
01:33:13 3 describing.

01:33:14 4 Q And that is rare.

01:33:15 5 A That is rare.

01:33:15 6 Q Okay. Now, with regard to the patient population who has
01:33:21 7 very high triglycerides, it's less rare for patients to have a
01:33:26 8 genetic predisposition to high triglycerides, and then there
01:33:33 9 are other factors that cause them to go above 500. Is that
01:33:38 10 fair?

01:33:38 11 A Yes.

01:33:38 12 Q Okay. And that's where diet and lifestyle can come into
01:33:42 13 play.

01:33:42 14 A Yes.

01:33:43 15 Q All right. Okay. Let's go to slide DX 3.13, which is
01:33:51 16 DX 1982, and I don't believe this is in evidence, so I would
01:33:57 17 move -- do you recognize this as Amarin's website for Vascepa?

01:34:01 18 A I don't know if I've seen this, but I would take your
01:34:04 19 word for it that it is. It looks like it.

01:34:06 20 MR KLEIN: I move to admit DX 1982.

01:34:11 21 MR. M. KENNEDY: No objection, Your Honor.

01:34:11 22 THE COURT: That request is granted.

01:34:11 23 (Defendants' Exhibit 1982 received in
01:34:14 evidence.)

01:34:16 24 BY MR. KLEIN:

01:34:17 25 Q Now, here you can see that -- and I'll represent to you

01:34:19 1 that we took this from Vascepa.com, and you'll see that the
01:34:25 2 title of this portion of the web page says what are the
01:34:29 3 causes?

01:34:30 4 A Yes.

01:34:31 5 Q And according to Amarin's Vascepa website, there are five
01:34:36 6 causes listed, right?

01:34:38 7 A There are five listed here, yes.

01:34:41 8 Q And the first one is diet. Do you see that?

01:34:43 9 A Yes.

01:34:43 10 Q And I circled "especially alcohol." You agree that diet,
01:34:48 11 especially alcohol, with be a cause of severe
01:34:51 12 hypertriglyceridemia, right?

01:34:52 13 A Yes.

01:34:52 14 Q Okay. And the second one is lack of exercise, that's
01:34:56 15 also a common cause of severe hypertriglyceridemia?

01:34:58 16 A It tends to be a contributing factor. I think -- I don't
01:35:03 17 think lack of exercise by itself is considered a primary
01:35:08 18 cause, but I think it would contribute so we recommend
01:35:10 19 exercise to help lower triglycerides.

01:35:13 20 Q It's normally discussed in combination with diet. Is
01:35:16 21 that fair?

01:35:17 22 A Yes.

01:35:17 23 Q And then the third cause is medical conditions, right?

01:35:20 24 A Yes.

01:35:21 25 Q And I think you talked about that, for example, a patient

01:35:24 1 could have diabetes and that might cause severe
01:35:28 2 hypertriglyceridemia?

01:35:28 3 A Yes.

01:35:29 4 Q But if the diabetes is controlled, that might address the
01:35:32 5 severe hypertriglyceridemia.

01:35:34 6 A That is the guidelines and my recommendation, yes.

01:35:37 7 Q Okay. And then there's specific drugs. I think talked
01:35:41 8 about that as well, right?

01:35:43 9 A Yes.

01:35:43 10 Q And we'll get back to that.

01:35:46 11 And then genetics is the fifth cause listed on
01:35:49 12 Vascepa.com, right?

01:35:51 13 A Right.

01:35:53 14 Q Now, the defendants' indication and labels are not
01:36:03 15 limited to addressing the genetic issues that we talked about
01:36:09 16 that can cause triglycerides to be way up in the 1,000, 2,000
01:36:15 17 area, right?

01:36:16 18 A That's correct.

01:36:16 19 Q Yeah. Defendants' labels would include very high
01:36:22 20 triglycerides caused by any of these five factors, diet,
01:36:26 21 exercise, medical condition, specific drugs, or genetics,
01:36:31 22 correct?

01:36:31 23 A No.

01:36:31 24 Q Okay. So you're saying that the Vascepa.com website is
01:36:36 25 incorrect?

01:36:37 1 A No. Vascepa -- this is saying what are causes of very
01:36:40 2 high triglycerides, and they list five different causes.

01:36:43 3 The label, and, again, the label taken in its
01:36:47 4 entirety, tells you to address diet and exercise first and
01:36:51 5 eliminate those causes, to address medical conditions and
01:36:55 6 eliminate those causes, to look for specific drugs and
01:37:01 7 eliminate those causes; and then, if their triglycerides are
01:37:05 8 still high, to treat.

01:37:06 9 So if you looked at your chart and you crossed out
01:37:09 10 those other four, the only thing left to use Vascepa on label
01:37:14 11 would be genetics.

01:37:16 12 Q Okay. I want to make sure I understand this testimony.

01:37:18 13 You're saying that the indication requires doctors
01:37:23 14 to eliminate the first four causes on Vascepa.com, diet,
01:37:29 15 exercise, medical conditions, specific drugs, and use the drug
01:37:32 16 only if genetics is the sole cause. Is that your testimony?

01:37:36 17 A No, I'm saying that the label eliminates those other 4,
01:37:40 18 and then says if severe hypertriglyceridemia still exists, you
01:37:45 19 then prescribe Vascepa.

01:37:49 20 Q Are you saying, Doctor, that if -- if a patient presents
01:37:55 21 to a physician, and has triglycerides of 550, and the doctor
01:38:01 22 says, "I -- I want you to go on a diet, and I want you to
01:38:05 23 exercise, and I want you to start Vascepa right away," you're
01:38:09 24 saying that's an off-label use?

01:38:11 25 A No. You're supposed to institute diet and exercise first

01:38:15 1 and then Vascepa.

01:38:17 2 Q Okay. But it's not an off-label use if the doctor at
01:38:21 3 that first visit says, "I want you to change your diet, I want
01:38:25 4 you to exercise, and I want you to fill this prescription,"
01:38:30 5 right, sir?

01:38:30 6 A I mean, you can interpret that as saying, well, I said
01:38:34 7 the word diet and exercise first so it preceded it, but that's
01:38:37 8 not the intent of the FDA nor the guidelines. The guidelines
01:38:40 9 say institute diet and exercise and then prescribe Vascepa.

01:38:45 10 So instituting, to me, is not saying, "Mr. Johnson,
01:38:48 11 you should really eat better. Here's a prescription."

01:38:52 12 I don't believe that meets the term institute, and
01:38:55 13 it's not how the guidelines are written. We just went through
01:38:58 14 the ATP III guidelines. They say to address diet first and
01:39:02 15 then prescribe Vascepa.

01:39:04 16 And I think the label is pretty clear in that
01:39:06 17 language that you should institute diet and exercise first
01:39:11 18 before initiating Vascepa.

01:39:12 19 There's literally a section, 2.1, that says what to
01:39:16 20 do before initiating Vascepa. So it's telling you to do that
01:39:20 21 specifically. That's not my interpretation. That's got to be
01:39:23 22 the exact way that the label is encouraging physician's use.

01:39:28 23 Q Okay. Well, let's start with this. The Vascepa labeling
01:39:31 24 is not limited to reducing triglycerides in patients who have
01:39:36 25 a genetic predisposition to high triglycerides, right?

01:39:40 1 A That's true.

01:39:41 2 Q Okay. And nothing in the Vascepa label discusses genetic
01:39:49 3 causes of severe hypertriglyceridemia?

01:39:51 4 A That's true.

01:39:52 5 Q And the cause of severe hypertriglyceridemia in most
01:39:56 6 patients is not solely genetics, right?

01:39:59 7 A Well, again, by the time we get to -- we're talking about
01:40:03 8 on-label use, I believe it is largely genetics. If we're
01:40:07 9 talking just about anybody who has ever had a fasting
01:40:10 10 triglyceride of 501 more, or 500 or more, that could be a
01:40:14 11 combination of factors, I agree with you.

01:40:16 12 Q Okay. Let's put aside whether it's on-label or off-label
01:40:20 13 now, and we'll talk turn that next.

01:40:22 14 A Sure.

01:40:22 15 Q Just doctors understand that when patient -- the patient
01:40:26 16 population that has very high triglycerides, a large portion
01:40:33 17 of that population has very high triglycerides for reasons not
01:40:41 18 solely related to genetics. Fair?

01:40:46 19 A Yes.

01:40:47 20 Q Okay. In fact, at least a third of the patient
01:40:51 21 population with severe hypertriglyceridemia has the condition
01:40:56 22 for reasons not solely related to genetics, right?

01:41:00 23 A I think that would probably be correct. Yes.

01:41:03 24 Q And the other causes would include things like diet and
01:41:07 25 exercise are not ideal, correct?

01:41:11 1 A Yes.

01:41:12 2 Q Okay. Let's go to -- let's fast forward and go to the
01:41:19 3 dosage and administration section because that's what you were
01:41:23 4 focusing on.

01:41:26 5 Okay. And this is DX 2256 for the record.

01:41:30 6 Do you recognize this as the dosage and
01:41:34 7 administration section from Hikma's proposed label?

01:41:37 8 A Yes.

01:41:38 9 Q And you testified that the dosage and administration
01:41:41 10 section instructs doctors to eliminate other causes of high
01:41:44 11 triglycerides before prescribing icosapent, right?

01:41:51 12 A Yes.

01:41:51 13 Q Okay. Let's walk through what each section says. The
01:41:53 14 title -- and I'm focusing on 2.1. That's what you're focusing
01:41:53 15 on, right?

01:41:53 16 A Yes.

01:41:58 17 Q The title says Prior to Initiation of Icosapent Ethyl,
01:42:02 18 right?

01:42:02 19 A Yes.

01:42:03 20 Q And then the first thing it says to do is assess lipid
01:42:06 21 levels before initiating therapy, and I think you testified
01:42:09 22 that, you know, that's -- that just makes sense, it's
01:42:12 23 standard, you have to take a test, right?

01:42:15 24 A Yes.

01:42:15 25 Q Okay. Then it says identify other causes, e.g.,

01:42:20 1 diabetes, hypothyroidism, or medications of high triglyceride
01:42:27 2 levels, and manage as appropriate, right?

01:42:29 3 A Yes.

01:42:29 4 Q So this is telling doctors look to see if there are other
01:42:33 5 causes, right?

01:42:34 6 A Yes.

01:42:34 7 Q And if the doctors identify other causes, the label
01:42:39 8 leaves it up to the discretion of the doctor to manage as the
01:42:42 9 doctor feels is appropriate, right?

01:42:45 10 A Yes.

01:42:46 11 Q Okay. The label is not telling, in this first bullet,
01:42:52 12 the label is not telling doctors don't give icosapent yet,
01:42:57 13 address those other factors first. Agreed?

01:43:00 14 A Correct.

01:43:01 15 Q Okay. And that bullet certainly isn't saying only give
01:43:08 16 icosapent if absolutely necessary and the only causes are
01:43:12 17 genetics, right?

01:43:15 18 A That's correct.

01:43:15 19 Q And when the label, 2.1, first bullet says manage as
01:43:22 20 appropriate, that is giving doctors wide discretion to do what
01:43:25 21 the doctor sees fit for the individual patient.

01:43:29 22 A Yes.

01:43:29 23 Q Okay. Let's go to the second bullet.

01:43:47 24 The second bullet says patients should engage in
01:43:51 25 appropriate nutritional intake and physical activity before

01:43:56 1 receiving icosapent ethyl which should continue during
01:44:01 2 treatment with icosapent ethyl, right?

01:44:02 3 A Yes.

01:44:03 4 Q And what this bullet is saying is that doctors should
01:44:07 5 make sure they don't use icosapent as a substitute for diet
01:44:13 6 and exercise, right?

01:44:14 7 A No, they're saying that patients should try a trial of
01:44:18 8 nutritional intake and physical activity before receiving
01:44:22 9 icosapent ethyl.

01:44:22 10 It says they should engage in appropriate
01:44:25 11 nutritional intake and physical activity before receiving the
01:44:29 12 drug.

01:44:29 13 So saying eat well, exercise, and here's a
01:44:33 14 prescription, would not be following Hikma's proposed label
01:44:39 15 because they wouldn't be engaging in any of those things
01:44:41 16 before receiving icosapent ethyl.

01:44:43 17 Q Okay.

01:44:43 18 A So I believe that if you don't give the patients a trial
01:44:47 19 of diet and exercise before receiving icosapent ethyl, that
01:44:50 20 that would be perceived as an off-label use of the drug.

01:44:54 21 Q Okay. So your opinion is that doctors should never
01:44:58 22 prescribe icosapent without first making sure that the
01:45:02 23 patients engage in diet and exercise?

01:45:05 24 A You can vary from the label. Doctors have discretion.
01:45:09 25 But the label specifically tells you that they should engage

01:45:13 1 first.

01:45:13 2 So if you are following the label, an on-label use
01:45:17 3 would be a trial of diet and exercise, we've discussed that a
01:45:21 4 few times today, and then if they fail appropriate diet and
01:45:24 5 exercise, then you prescribe icosapent ethyl.

01:45:28 6 Q That's not how you practice, right?

01:45:30 7 A That's how I largely practice.

01:45:32 8 Q When a patient comes to see you and presents with very
01:45:35 9 high triglycerides, you hold off on prescribing Vascepa until
01:45:40 10 the next visit?

01:45:44 11 A If their triglyceride are 550, like in your example, and
01:45:47 12 they have a terrible diet, yes. I would say let's clean up
01:45:52 13 your diet and exercise and see if we don't get there without
01:45:53 14 therapy, and if we don't get there without therapy, then I'm
01:45:54 15 going to need to prescribe a medication.

01:45:56 16 That's how we all prescribe therapy. That's the
01:45:58 17 common use of all treatments. Blood pressure pills are the
01:46:02 18 same. When I see somebody with high blood pressure, and they
01:46:06 19 have a high salt diet, I say let's try diet and exercise and
01:46:07 20 see if your blood pressure comes down, and if that fails, I'm
01:46:10 21 going to have to write you a prescription for a blood pressure
01:46:13 22 pill.

01:46:14 23 Q Okay.

01:46:14 24 A That's the way the FDA literally says -- there's no -- I
01:46:17 25 don't think there's any interpretation here. Patients should

01:46:21 1 engage in appropriate nutritional intake and physical activity
01:46:25 2 before receiving icosapent ethyl. Your company wrote a --
01:46:28 3 very clear instructions for doctors to follow.

01:46:31 4 Q Okay. Doctor, you prescribe icosapent the first time you
01:46:37 5 see a patient who presents with very high triglycerides,
01:46:42 6 right? That happens?

01:46:42 7 A Sometimes, sure.

01:46:43 8 Q Probably most of the time, right?

01:46:45 9 A I don't know. I haven't looked back exactly. But some
01:46:48 10 of my patients are already engaged in appropriate nutritional
01:46:53 11 activity and nutritional intake when they first see me.

01:46:56 12 I described a scenario today of a young woman who is
01:46:59 13 already doing all the right things, and her triglycerides are
01:47:01 14 too high. So she already engaged in appropriate nutritional
01:47:06 15 intake and physical activity before receiving icosapent ethyl,
01:47:06 16 and then I prescribed it. That's my first visit, but the
01:47:12 17 patient is already doing what the label instructs me to do.

01:47:13 18 Q Okay. And pancreatitis can be a life-threatening
01:47:17 19 condition, right?

01:47:18 20 A Yes.

01:47:18 21 Q And if a patient presents to you with 650, for example,
01:47:24 22 you're not going to hold off on giving that patient Vascepa
01:47:28 23 for -- until you see the patient a second time, you're going
01:47:32 24 to prescribe Vascepa right away, correct?

01:47:34 25 A In most cases, yes.

01:47:39 1 Q Yes. And are you really telling the Court that the
01:47:42 2 Vascepa label and defendants' label will make it an off-label
01:47:48 3 use if a doctor prescribes Vascepa at the same time as the
01:47:52 4 doctor instructs the patients to improve their exercise and
01:47:57 5 diet?

01:47:57 6 A I believe, and I think the label is explicitly clear
01:48:02 7 here, that if you think diet and exercise is all they need,
01:48:06 8 then you should not be prescribing Vascepa.

01:48:09 9 So in your first example where the triglycerides are
01:48:11 10 550, and they have a terrible diet, I would not, and the label
01:48:15 11 would not advocate to put them on Vascepa because it is highly
01:48:19 12 likely that diet and exercise intervention alone will not
01:48:23 13 achieve the target.

01:48:25 14 Now, if somebody has triglycerides of 2,000, and
01:48:28 15 their blood is turning white from fats, then I do not wait.
01:48:33 16 But I think that that could be perceived as an off-label use.

01:48:37 17 Regardless, the vast majority of patients we see,
01:48:40 18 we're supposed to first address nutritional intake and
01:48:43 19 physical activity before receiving icosapent ethyl, and then,
01:48:47 20 if they don't get under 500, we then prescribe them the
01:48:52 21 therapy.

01:48:52 22 That's also how the MARINE trial was done which I
01:48:55 23 testified to this morning on how we did the MARINE trial, how
01:48:59 24 the trial was performed by having a 6-to 9-week trial of diet
01:49:04 25 and exercise before prescribing therapy.

01:49:07 1 Q Okay. Let's take another look at the language in the
01:49:10 2 second bullet.

01:49:12 3 So would you -- your entire opinion here is based on
01:49:18 4 one term, the term "before," right?

01:49:20 5 A No, my entire opinion is based on my experience,
01:49:24 6 treatment, and training. The word "before" --

01:49:25 7 Q No, no, hold on. Just to be clear --

01:49:27 8 A -- is contributory towards that. My opinion is never
01:49:33 9 based on a single word.

01:49:33 10 Q No, no, just --

01:49:34 11 A I want to be clear for the court.

01:49:35 12 Q Okay. All right. But your opinion with regard to what's
01:49:38 13 on-label and off-label in view of 2.1 -- bullet 2, turns on
01:49:43 14 the word before, right?

01:49:44 15 A In this one scenario, yes.

01:49:47 16 Q I mean, if that said "with," you would have a different
01:49:49 17 opinion, right?

01:49:49 18 A I think the implication would be different, yes.

01:49:52 19 Q And when 2.1 bullet two uses the term before, it doesn't
01:49:57 20 specify any time frame, right?

01:49:59 21 A That's true.

01:50:00 22 Q It doesn't say, doctors, make sure that the patients
01:50:05 23 actually improve their diet and exercise for 12 weeks, come
01:50:10 24 back, and then if it's clear that the causes are genetic, then
01:50:13 25 you may prescribe icosapent. That's not what the label is

01:50:18 1 saying, right?

01:50:19 2 A It doesn't give a time period, that's correct.

01:50:21 3 Q And, in fact, and I think you mentioned something like
01:50:23 4 this earlier, if the doctor told the patients I want you to --
01:50:28 5 here's a diet, I want you to follow it, here's exercise,
01:50:31 6 regimen I want you to follow it, here's a prescription, fill
01:50:34 7 it when you can get to a pharmacy, that would be following the
01:50:38 8 dosage and administration section 2.1, bullet 2, correct?

01:50:43 9 A No.

01:50:43 10 Q And why is that?

01:50:45 11 A Another word in the label it says engage, so they should
01:50:51 12 engage in appropriate nutritional intake and physical
01:50:54 13 activity. It doesn't say a doctor should advise that you go
01:50:58 14 on diet and exercise, and here's a prescription. It says that
01:51:02 15 they should engage in appropriate nutritional intake and
01:51:06 16 physical activity before receiving icosapent ethyl.

01:51:09 17 I don't think you can change the meaning of that. I
01:51:11 18 think doctors would read that and understand that you should
01:51:14 19 give them a trial. It doesn't have to be exactly 12 weeks as
01:51:17 20 you outlined in your previous example, but you need to give
01:51:21 21 them a trial of diet and exercise, and if they fail that, then
01:51:25 22 they can receive icosapent ethyl if their triglycerides are
01:51:28 23 still above 500.

01:51:30 24 Q Now, Dr. Budoff, the most common practice is for doctors
01:51:37 25 to prescribe icosapent as a first step for patients with

01:51:43 1 triglycerides above 500, correct?

01:51:45 2 A I don't know that.

01:51:46 3 Q Okay. Actually you do. Let's go to DX 1554, paragraph
01:51:54 4 56. Let's go first to the first page so we can identify the
01:52:01 5 document.

01:52:05 6 Okay. You recognize DX 1554 as your opening report?

01:52:10 7 A Yes.

01:52:13 8 Q Okay. Now let's go to page 17, paragraph 56.

01:52:21 9 A I'm sorry, what paragraph?

01:52:23 10 Q Paragraph 56.

01:52:24 11 A Okay. It's not on the screen?

01:52:26 12 Q It will be there in a second.

01:52:29 13 A Sure.

01:52:32 14 MR KLEIN: This is the reply? Do I have the
01:52:34 15 wrong document?

01:52:37 16 No, this is right.

01:52:37 17 BY MR. KLEIN:

01:52:39 18 Q Okay. Here, in your opening report, you said,

01:52:43 19 "For elevated lipids, therapy guidelines,
01:52:45 20 including ATP III, recommend diet and lifestyle
01:52:49 21 modification, and for patients with triglycerides of
01:52:54 22 500 milligrams per deciliter or higher, given the
01:52:57 23 serious risk of pancreatitis and a recognition that
01:53:01 24 lifestyle counseling alone is often insufficient for
01:53:05 25 these patients, physicians most commonly recommend a

01:53:08 1 triglyceride-lowering medication, along with
01:53:10 2 lifestyle counseling, as the first step."

01:53:13 3 Was that in your report, sir?

01:53:15 4 A No, that's citing ATP III, that's correct. That's 2002.
01:53:20 5 I don't believe that's an on-label use.

01:53:24 6 Q Okay. So you're saying this statement in your opening
01:53:27 7 report is inaccurate?

01:53:29 8 A No, I'm not saying that it's inaccurate at all. I'm
01:53:32 9 saying that it's -- I don't perceive it to be an on-label use
01:53:35 10 if you prescribe the drug at the same time as diet and
01:53:39 11 exercise and you don't have them engage in nutritional intake
01:53:45 12 and appropriate physical activity before receiving icosapent
01:53:49 13 ethyl.

01:53:49 14 Q Okay. Let's take a look at your reply report, and you
01:53:53 15 submitted a reply expert report after Dr. Sheinberg responded
01:53:58 16 to your report, right?

01:54:00 17 A Yes.

01:54:00 18 Q So this is after Dr. Sheinberg raised the 12-week
01:54:05 19 noninfringement defense, right?

01:54:06 20 A Yes.

01:54:07 21 Q Okay. And you recognize DX 1556 is your reply report?

01:54:12 22 A Yes.

01:54:12 23 Q Okay. Let's first take a look at paragraph 54.

01:54:37 24 In paragraph 54 of your reply report you said, "I
01:55:19 25 disagree that clinicians would read the indications and usage

01:55:23 1 section as encouraging clinicians to treat
01:55:28 2 hypertriglyceridemia by providing the patients with a
01:55:28 3 prescription for Vascepa or one of defendants' proposed ANDA
01:55:35 4 products but instruct the patient not to begin taking the
01:55:38 5 medication until after improving their diet and exercise
01:55:42 6 regimen over the course of 4 to 6 weeks."

01:55:44 7 Right? Is that something you said in your reply
01:55:46 8 report in response to Dr. Sheinberg's report?

01:55:49 9 A Yes.

01:55:50 10 Q Okay. Let's also take a look at paragraph 57 of your
01:55:56 11 reply report.

01:56:02 12 All right. In paragraph 57, you start off by
01:56:15 13 talking about the treatment guidelines, and in the second
01:56:18 14 sentence you say,

01:56:19 15 "The treatment guidelines therefore advise
01:56:21 16 that clinicians immediately treat severely
01:56:25 17 hypertriglyceridemic patients with triglyceride-
01:56:28 18 lowering pharmacotherapies."

01:56:31 19 Right? Is that what you said?

01:56:33 20 A Yes.

01:56:34 21 Q Immediately treat, right?

01:56:36 22 A Yes.

01:56:36 23 Q Okay. And if we go to paragraph 209 of your reply
01:56:47 24 report, here you say that,

01:57:12 25 "Statements in the label acknowledge that

01:57:14 1 clinicians will generally recommend to their severely
01:57:18 2 hypertriglyceridemic patients that they improve their
01:57:21 3 diet or improve or begin an exercise regimen.
01:57:25 4 However, in cases where the risk of pancreatitis is
01:57:28 5 judged sufficiently immediate, pharmacotherapy will
01:57:32 6 begin immediately."

01:57:34 7 This was in your reply report as well?

01:57:36 8 A Yes, that's exactly the scenario I just gave you. I said
01:57:40 9 if the triglyceride are superhigh --

01:57:42 10 Q Sir, I -- Doctor, I just asked you whether that was in
01:57:45 11 your report.

01:57:45 12 A Okay. I was just trying to put it in context, but, yes.

01:57:49 13 Q Okay. And according to ATP III, if patients have
01:57:53 14 triglycerides above 500, they're at risk for pancreatitis,
01:57:58 15 correct?

01:57:58 16 A Yes, they are at risk for pancreatitis.

01:58:01 17 Q And putting aside all of your testimony with regard to
01:58:14 18 the dosage and administration section that we were talking
01:58:17 19 about, a clinician -- it would be consistent with the Vascepa
01:58:21 20 labeling, and thus defendants' labels, for a doctor to
01:58:25 21 prescribe icosapent ethyl for fewer than 12 weeks, correct?

01:58:29 22 A Yes.

01:58:34 23 MR. KLEIN: Now, we were talking about the
01:58:46 24 various causes -- can you go back to the PowerPoint and
01:58:50 25 DDX 3.14.

01:58:50 1

01:58:50 2 BY MR. KLEIN:

01:58:57 3 Q We were talking about various causes of severe
01:58:57 4 hypertriglyceridemia, and we looked at the Vascepa.com
01:58:59 5 website. Do you remember that?

01:59:00 6 A Yes.

01:59:00 7 Q Okay. I want to now turn to the Miller article which you
01:59:05 8 talked about on direct. Do you remember that?

01:59:07 9 A Yes.

01:59:08 10 MR. KLEIN: Okay. And for the record, I'm
01:59:11 11 referring to DX 1632, and I believe the same document PX 269
01:59:19 12 has already been admitted, but for the -- to avoid any
01:59:24 13 confusion we'll move to admit DX 1632.

01:59:28 14 MR. M. KENNEDY: No objection.

01:59:29 15 THE COURT: 1632 is admitted.

01:59:29 16 (Defendants' Exhibit 1632 received in
01:59:32 evidence.)

01:59:32 17 BY MR. KLEIN:

01:59:33 18 Q And we're at 1632, page 11. Do you remember talking
01:59:36 19 about this?

01:59:36 20 A Yes.

01:59:37 21 Q Okay. And you understand -- do you understand that
01:59:41 22 Dr. Miller was actually Amarin's claim construction expert in
01:59:46 23 this case?

01:59:47 24 A I'm not aware of that, but I'll take your word for it.

01:59:50 25 Q Okay. So looking at table 5, this lists causes of very

01:59:56 1 high triglycerides that may be associated with pancreatitis,
02:00:00 2 right?

02:00:01 3 A Yes.

02:00:02 4 Q Okay. And I highlighted a couple of these causes:
02:00:08 5 Pregnancy, especially in the third trimester. Do you see
02:00:11 6 that?

02:00:11 7 A Yes.

02:00:11 8 Q Can we agree that pregnancy in the third trimester is not
02:00:16 9 a chronic condition?

02:00:17 10 A That's correct.

02:00:18 11 Q And certain drugs cause very high triglycerides, right?

02:00:21 12 A Yes.

02:00:21 13 Q And some of these drugs can be taken for less than 12
02:00:26 14 weeks, right?

02:00:27 15 A Yes.

02:00:28 16 Q For example, steroids?

02:00:30 17 A Yes.

02:00:31 18 Q Anything else?

02:00:31 19 A Steroids are probably the best example on this list of a
02:00:37 20 drug that's often used for short term therapy, maybe
02:00:41 21 Interferon as well.

02:00:42 22 Q And then diet, including alcohol, excess, we talked about
02:00:46 23 that, right?

02:00:46 24 A Yes.

02:00:46 25 Q And then a high saturated fat diet?

02:00:49 1 A Yes.

02:00:50 2 Q And eating high saturated fat food is not a chronic
02:00:55 3 condition, right?

02:00:56 4 A It often is in the United States, but -- yes, it's not.

02:01:01 5 Q You would like to think that --

02:01:02 6 A It doesn't have to be.

02:01:04 7 Q If you tell people they'll die if they don't stop eating
02:01:08 8 MacDonald's, they'll listen to you?

02:01:10 9 A Unfortunately not all the time, but, yes.

02:01:13 10 Q Okay. And diseases is up there too. As we talked about
02:01:17 11 some diseases can cause severe hypertriglyceridemia if they're
02:01:21 12 not controlled, right?

02:01:22 13 A That's correct.

02:01:23 14 Q And triglycerides can fluctuate based on factors such as
02:01:28 15 diet and exercise, right?

02:01:30 16 A Yes.

02:01:31 17 Q And in fact a patient's triglyceride levels can vary
02:01:34 18 significantly based on lifestyle and medication changes,
02:01:38 19 right?

02:01:38 20 A Yes.

02:01:39 21 Q Continuing through this article, we're at DDX 3.15, and
02:01:46 22 we're on page 20 of DX 1632, this slide says a weight loss of
02:01:52 23 5 to 10 percent results in a 20 percent decrease in
02:01:56 24 triglycerides. That's a true statement, right, sir?

02:02:00 25 A Yes.

02:02:01 1 Q Okay. Then moving to DX 1632, page 22, DDX 3.16, the
02:02:11 2 Miller reference says Mediterranean style diet versus a low
02:02:16 3 fat diet is more commonly associated with an approximately 10
02:02:21 4 to 15 percent lowering of triglycerides and a reduced
02:02:27 5 prevalence of hypertriglyceridemia, right?

02:02:29 6 A Yes.

02:02:29 7 Q That's true as well?

02:02:31 8 A Yes.

02:02:31 9 Q And if we go to DX 1632, pages 23 and 24, DDX 3.17,
02:02:42 10 Dr. Miller says,

02:02:43 11 "Ingestion of one ounce per day would
02:02:46 12 correspond to a 5 to 10 percent higher triglyceride
02:02:51 13 concentration than found in nondrinkers."

02:02:54 14 Is that correct?

02:02:55 15 A That's an average, but, yes.

02:02:57 16 Q Okay. On page 24 of DX 1632, DDX 3.18, Dr. Miller says,
02:03:05 17 ""Optimization of nutrition-related practices
02:03:08 18 can result in a marked triglyceride-lowering effect
02:03:11 19 that ranges between 20 and 50 percent," right?

02:03:14 20 A Yes.

02:03:15 21 Q And on page 27 of DX 1632, which is DDX 3.19, Dr. Miller
02:03:24 22 says,

02:03:24 23 ""Reductions of 50 percent or more in
02:03:27 24 triglyceride levels may be attained through intensive
02:03:31 25 therapeutic lifestyle change."

02:03:33 1 Do you agree with that?

02:03:35 2 A I have not seen that, but, yes, I agree.

02:03:36 3 Q Okay. But you understand that what Dr. Miller is saying
02:03:40 4 is, he's saying no drug therapy can get you this, right? You
02:03:46 5 can get this result without drugs.

02:03:48 6 A Yes.

02:03:48 7 Q And so a patient who presents with triglyceride levels of
02:03:54 8 550, for example, could eventually reduce the triglyceride
02:03:59 9 levels down to 275, roughly, through intensive therapeutic
02:04:06 10 lifestyle changes alone. Right?

02:04:09 11 A If you took a terrible patient and made them a perfect
02:04:12 12 patient, yes.

02:04:13 13 Q Okay. But, I mean, that's going to take some time,
02:04:15 14 right?

02:04:15 15 A But it's also not always the scenario. In your scenario
02:04:20 16 to do all of these things, they have to be overweight,
02:04:23 17 nonexercising, drinking person who has a terrible diet to be
02:04:27 18 able to make all of those lifestyle changes, and then, in that
02:04:30 19 scenario, you go from very high to high. But, yes, that is
02:04:34 20 possible.

02:04:35 21 Q Okay. And so the mere fact that a patient presents to
02:04:39 22 the doctor with triglycerides over 500 does not necessarily
02:04:43 23 mean the patient requires drug therapy, right?

02:04:47 24 A Absolutely.

02:04:47 25 Q Now, Doctor, half of your patients with severe

02:05:03 1 hypertriglyceridemia have the condition due to poor lifestyle
02:05:08 2 choices, correct?

02:05:09 3 A Let's say poor lifestyle choices contribute to the
02:05:12 4 condition.

02:05:13 5 Q Okay. Because -- and you say that because the patients
02:05:16 6 may be genetically predisposed to high triglycerides.

02:05:20 7 A Yes.

02:05:20 8 Q And, again, these lifestyle causes are not necessarily
02:05:26 9 chronic, right?

02:05:27 10 A And I think to be accurate and consistent, I think we
02:05:30 11 said a third earlier, so I would like to stay with that number
02:05:33 12 if we could.

02:05:34 13 So I don't want my -- my testimony to be changing
02:05:37 14 during this transcript. We said a third of patients earlier.
02:05:41 15 I think we'll stick with that number if that's okay with you.

02:05:44 16 Q Right. We don't want your testimony to change.

02:05:47 17 A Right.

02:05:47 18 Q So you would say maybe half of your patients have poor
02:05:51 19 lifestyle that has pushed the patient's triglycerides the
02:05:54 20 wrong way, right?

02:05:55 21 A Yeah, of the people I see, probably half of them are not
02:05:59 22 eating optimally when I see them, that's correct.

02:06:02 23 Q And that's contributing to the very high triglyceride
02:06:06 24 level?

02:06:06 25 A Yes.

02:06:07 1 Q And we talked -- you talked about binge drinking, right?

02:06:12 2 A Yes.

02:06:14 3 Q Binge drinking can cause spikes in some patients above
02:06:20 4 550.

02:06:20 5 A Above 500, yes.

02:06:21 6 Q I'm sorry, above 500.

02:06:23 7 And to be clear, and I think you made this point,
02:06:25 8 you're not saying, and I think you used the example in the
02:06:28 9 deposition, you're not saying at Mardi Gras everyone walking
02:06:32 10 around is going to have very high triglycerides, right?

02:06:35 11 A Very few will.

02:06:36 12 Q Yeah, you're saying that there are patients that are
02:06:40 13 predisposed to high triglycerides, have never had very high
02:06:44 14 triglycerides, but they engage in binge drinking and their
02:06:47 15 triglycerides spike above 500, correct?

02:06:50 16 A Yes.

02:06:51 17 Q Okay. And these types of patients can get their
02:06:59 18 triglyceride levels below 500 by cutting out the alcohol,
02:07:03 19 right?

02:07:03 20 A If they're sufficiently close to 500, yes.

02:07:07 21 Q And doctors know this, right?

02:07:10 22 A Yes.

02:07:11 23 Q And so a doctor -- I mean, so a patient who presents with
02:07:18 24 triglycerides let's say close to 600, and you identify at
02:07:24 25 least one contributing cause as alcohol, could potentially

02:07:29 1 benefit from taking icosapent for a short time while the
02:07:34 2 patient goes off alcohol, and then could stop the treatment if
02:07:38 3 it turns out the patient is now below 500 after taking out the
02:07:42 4 alcohol, correct?

02:07:43 5 A I think that's completely unknown, that hypothetical. We
02:07:47 6 have no idea what the short term benefits of icosapent ethyl
02:07:51 7 are in terms of pancreatitis, and I think the label
02:07:55 8 specifically calls that out, that the effect on pancreatitis
02:07:59 9 is not known.

02:08:00 10 Q Okay. And so a doctor who sees a patient with
02:08:03 11 triglycerides above 500 due to binge drinking could tell the
02:08:07 12 patient stop drinking but also take Vascepa to help avoid
02:08:12 13 pancreatitis, right?

02:08:13 14 A I doubt anybody would ever do that in practice, but that
02:08:17 15 is a hypothetical situation.

02:08:19 16 Q And that hypothetical would be on-label, right?

02:08:21 17 A No, it would be off-label because they're not engaging in
02:08:25 18 proper nutritional activity before initiating Vascepa therapy
02:08:32 19 unless you think that the words saying stop drinking means
02:08:36 20 that they stopped drinking.

02:08:37 21 And I can tell you that the words stop smoking do
02:08:40 22 not imply that the patient has stopped smoking. So they need
02:08:43 23 to engage, your label, engage in appropriate nutritional
02:08:48 24 activity before initiating icosapent ethyl. I'm -- it's not
02:08:51 25 my terminology. This is what you're putting forth.

02:08:55 1 Q Okay. It would not be off-label if a patient who had
02:09:00 2 triglycerides above 500 because of binge drinking, for the
02:09:04 3 doctor to say, "Stop drinking, but also take Vascepa because
02:09:08 4 you have a risk of pancreatitis, and we want to get your
02:09:12 5 triglycerides down immediately," correct?

02:09:14 6 A I think that's a probably a borderline off-label use, but
02:09:19 7 I would say it's appropriate to do that if their triglycerides
02:09:22 8 are very, very high and the risk of acute pancreatitis is
02:09:25 9 eminent.

02:09:26 10 Q Doctor you were deposed in it case, right?

02:09:29 11 A Yes.

02:09:30 12 MR. KLEIN: You should have a copy of your
02:09:31 13 deposition, but we'll play a video clip. Mr. Gross, can you
02:09:35 14 play page 196, page 10 -- I'm sorry, page 196, lines 10 to 25.

02:09:43 15 (Deposition video played.)

02:10:30 16 BY MR. KLEIN:

02:10:30 17 Q Sir, was that your testimony?

02:10:31 18 A Yes.

02:10:31 19 Q Okay. And can we agree that a patient with severe
02:10:39 20 hypertriglyceridemia does not necessarily require indefinite
02:10:43 21 drug therapy?

02:10:44 22 A Yes.

02:10:45 23 Q Okay. And many patients with severe hypertriglyceridemia
02:10:49 24 don't require any drug therapy at all, right?

02:10:52 25 A That's correct.

02:10:53 1 Q And that's in part because weight reduction and exercise
02:10:59 2 can reduce triglycerides in many patients, right?

02:11:03 3 A In some patients, yes.

02:11:05 4 Q Some patients. Okay.

02:11:07 5 Let's take another look at the indication. We're on
02:11:10 6 DX 2256, and it's DDX 3.20.

02:11:15 7 We talked about this a little bit before, but the
02:11:18 8 indication is for use as an adjunct to diet, right?

02:11:22 9 A Yes.

02:11:23 10 Q And adjunct in this context means in addition to diet?

02:11:27 11 A Yes.

02:11:28 12 Q And so it's pretty clear that FDA did not approve Vascepa
02:11:32 13 to replace diet, right?

02:11:34 14 A Yes.

02:11:34 15 Q And the label is telling doctors that diet is the primary
02:11:39 16 way to treat severe hypertriglyceridemia, right?

02:11:42 17 A I think that's overstating the label. Diet and Vascepa
02:11:46 18 reduces triglyceride levels. I don't think it says diet alone
02:11:50 19 in the label, at least I'm not aware of diet alone being the
02:11:54 20 primary way to treat severe hypertriglyceridemia appearing
02:11:55 21 anywhere in the label.

02:11:56 22 Q Doctor, I thought your testimony is that when a patient
02:11:59 23 presents, you're supposed to put them on a diet first.

02:12:02 24 A Yes, but it doesn't usually work.

02:12:04 25 Q Okay.

02:12:05 1 A So it's not predominant way of doing it. It works in
02:12:10 2 20 percent of patients, and in 80 percent of patients it
02:12:13 3 fails. So the predominant way is to use drug therapy just to
02:12:17 4 go back to the your initial question.

02:12:19 5 Q Right. But if you look at the indication, the indication
02:12:22 6 is clearly telling doctors that they can use Vascepa as an
02:12:25 7 adjunct to diet according to the doctor's discretion, right?

02:12:30 8 A Yes.

02:12:30 9 Q And in your personal practice you have seen diet and
02:12:34 10 exercise alone without any drugs decrease triglyceride levels
02:12:38 11 by about 25 percent, right?

02:12:39 12 A Yes.

02:12:40 13 Q And you're familiar, you talked about the MARINE study on
02:12:45 14 direct, right?

02:12:45 15 A Yes.

02:12:46 16 Q Let's talk about the MARINE study, and this is DX 1694,
02:12:51 17 page 24, DDX 3.21. This is already admitted.

02:12:56 18 In MARINE, patients were given diet and exercise for
02:13:01 19 a period of four to six weeks as a lead-in before the 12-week
02:13:07 20 study began, right?

02:13:09 21 A Yes.

02:13:09 22 Q And then, if we go to DDX 3.22 on the same page, there
02:13:20 23 was then a two- to three-week qualifying period, right?

02:13:23 24 A Yes.

02:13:23 25 Q And this was to make sure that the patients who were

02:13:27 1 going to enter the 12-week MARINE study had severe
02:13:32 2 hypertriglyceridemia, right?

02:13:34 3 A Yes.

02:13:34 4 Q And had severe hypertriglyceridemia that was not
02:13:40 5 addressed by diet and exercise in the four- to six-week
02:13:40 6 lead-in, right?

02:13:40 7 A Yes.

02:13:47 8 Q And so in this scenario, in the MARINE study, Amarin
02:13:52 9 tried diet and exercise in a number of patients, and then a
02:13:56 10 number of those patients didn't qualify, right?

02:13:58 11 A Right.

02:13:58 12 Q And that's because diet and exercise worked for them,
02:14:02 13 correct?

02:14:02 14 A Yes. That's one reason. There's other reasons why
02:14:05 15 people don't qualify, but, yes, that's the primary exclusion.

02:14:08 16 Q Okay. Fair enough.

02:14:09 17 And then during these two to three weeks Amarin is
02:14:13 18 looking at the remaining population and saying these patients
02:14:17 19 qualify for the 12-week trial, right?

02:14:20 20 A Yes.

02:14:20 21 Q And then we're on DDX 3.23. It's the same document,
02:14:30 22 page 27, I just changed the highlighting.

02:14:35 23 Only patients with triglycerides above 500 after
02:14:38 24 this four to six-week lead-in and the two to three-week
02:14:42 25 qualifying period entered into the 12-week safety and efficacy

02:14:46 1 MARINE trial, right?

02:14:48 2 A Yes.

02:14:48 3 Q And, in your view, Vascepa is indicated for those
02:14:53 4 patients who qualified for the MARINE study, right?

02:14:56 5 A Yes.

02:14:56 6 Q These are patients that went through some diet and
02:14:59 7 exercise and still didn't get their triglycerides below 500 in
02:15:03 8 that period of time, right?

02:15:04 9 A Exactly.

02:15:05 10 Q And you agree that Vascepa is indicated for those
02:15:08 11 patients who qualified for the MARINE trial, right?

02:15:11 12 A Yes.

02:15:12 13 Q And defendants' labels will be directed to this patient
02:15:15 14 population as well?

02:15:16 15 A Yes.

02:15:17 16 Q And all of the patients who qualified for the MARINE
02:15:22 17 study could benefit from icosapent treatment, right?

02:15:26 18 A Potentially, yes.

02:15:29 19 Q And your position is that all patients who qualified for
02:15:34 20 the 12-week MARINE study had severe hypertriglyceridemia,
02:15:38 21 right?

02:15:39 22 A Yes, at baseline visit.

02:15:42 23 Q Now, Doctor, some of the patients that qualified for the
02:15:46 24 MARINE study were put into a placebo group, right?

02:15:50 25 A Yes.

02:15:51 1 Q Okay. And all of the patients in the placebo group had
02:15:54 2 triglycerides above 500.

02:15:55 3 A Yes.

02:15:56 4 Q Okay. And let me change documents. This is DX 1701,
02:16:02 5 page 51. This is from the medical review. Do you remember
02:16:05 6 looking at that?

02:16:06 7 A I've seen it. I didn't review it in great detail, but,
02:16:10 8 yes, I've seen this document.

02:16:11 9 Q You used this on your direct examination, right, the FDA
02:16:16 10 medical review?

02:16:17 11 A I think I referenced one section of it, but, yes.

02:16:20 12 Q Okay. And for the record this is DDX 3.24.

02:16:24 13 The subjects in the placebo group in MARINE were
02:16:28 14 instructed to maintain the diet and exercise regimen
02:16:31 15 throughout the entire 12-week period, right?

02:16:33 16 A Yes.

02:16:34 17 Q And those -- so those patients in the placebo group
02:16:39 18 didn't get any Vascepa.

02:16:41 19 A That's correct.

02:16:42 20 Q And after 12 weeks of continuing a diet and exercise
02:16:47 21 regimen, 21 percent of those subjects in the placebo group, 16
02:16:52 22 out of 75, were able to achieve and maintain triglyceride
02:16:56 23 levels below 500 milligrams per deciliter by the study
02:17:02 24 endpoint, correct?

02:17:03 25 A Yes.

02:17:03 1 Q And that's the green bar on DDX 3.24, right?

02:17:08 2 A Yes.

02:17:08 3 Q And so according to MARINE, about 21 percent of patients
02:17:15 4 falling within the scope of defendants' indication can achieve
02:17:18 5 and maintain triglyceride levels below 500 with diet and
02:17:22 6 exercise alone, correct?

02:17:24 7 A Yes.

02:17:24 8 Q And these patients didn't need any Vascepa to get below
02:17:29 9 500, right?

02:17:30 10 A That's correct.

02:17:31 11 Q And these patients could benefit from a short course of
02:17:34 12 icosapent given that they qualified for the MARINE study, but
02:17:39 13 long-term they wouldn't require Vascepa to maintain levels
02:17:44 14 below 500, right?

02:17:46 15 A How would they benefit? I don't understand the question.

02:17:49 16 Q Well, these are patients who, in the first four to
02:17:57 17 six weeks tried diet and exercise alone and it didn't work,
02:18:01 18 right?

02:18:01 19 A Right.

02:18:05 20 Q Okay. And so if these patients in the placebo group were
02:18:09 21 given Vascepa immediately, their triglyceride levels would
02:18:14 22 drop more quickly, right?

02:18:15 23 A Probably, yes.

02:18:17 24 Q And by the time you get into the 12-week period, they
02:18:22 25 wouldn't even need Vascepa, according to MARINE, to maintain

02:18:26 1 levels above 500, right?

02:18:28 2 A You're talking about those 21 percent.

02:18:31 3 Q Correct.

02:18:31 4 A Yes.

02:18:32 5 Q And consistent with MARINE, about 20 percent of your
02:18:38 6 patients with severe hypertriglyceridemia are able to reduce
02:18:42 7 their triglyceride levels below 500 with diet and exercise
02:18:47 8 alone, right?

02:18:48 9 A Yes.

02:18:48 10 Q And so about one-fifth or 20 percent of patients with
02:18:53 11 very high triglyceride levels don't necessarily need any drug
02:18:58 12 therapy to get their levels below 500, right?

02:19:01 13 A That's correct.

02:19:03 14 Q Now, even in those patients who don't necessarily need
02:19:07 15 Vascepa, you still sometimes prescribe Vascepa, right?

02:19:11 16 A I would never prescribe a drug that I don't perceive they
02:19:15 17 need, no.

02:19:15 18 Q Well, you -- well, let's come back to that.

02:19:26 19 Now, some of your patients who were able to reduce
02:19:39 20 triglycerides below 500 with diet and exercise alone say no
02:19:44 21 thanks when you suggest Vascepa, right?

02:19:46 22 A Right. They can't get it or they don't want to take it.
02:19:50 23 That's correct.

02:19:51 24 Q And this happens with some frequency because you have a
02:19:54 25 lot of patients who don't like taking drugs unless they need

02:19:58 1 to, right?

02:19:58 2 A Yes.

02:19:58 3 Q You practice in California so you may see that more often
02:20:02 4 than others.

02:20:02 5 A Yes.

02:20:03 6 Q Okay. And the dosing regimen for Vascepa is four pills a
02:20:07 7 day twice a day.

02:20:08 8 A Four pills a day total; two twice a day.

02:20:11 9 Q That's what I meant. I'm sorry. Two pills in the
02:20:13 10 morning and two in the evening, right?

02:20:15 11 A Yes.

02:20:16 12 Q That's an inconvenient dosing regimen for many patients,
02:20:20 13 right?

02:20:21 14 A Yes.

02:20:21 15 Q And so you have patients who start on Vascepa therapy and
02:20:32 16 then stop.

02:20:32 17 A Yes.

02:20:32 18 Q About ten percent of your patients stop taking Vascepa
02:20:36 19 for various reasons, right?

02:20:38 20 A Yes.

02:20:38 21 Q And you agree that patients could follow the Vascepa
02:20:47 22 labeling and effectively treat patients with severe
02:20:51 23 hypertriglyceridemia for less than 12 weeks, right?

02:20:54 24 A Can you say that again? I'm sorry.

02:20:56 25 Q Okay. You agree that physicians could follow the Vascepa

02:21:02 1 labeling and treat severely hypertriglyceridemic patients with
02:21:05 2 Vascepa 4 grams per day for fewer than 12 weeks and achieve an
02:21:10 3 effect, correct?

02:21:11 4 A Yes.

02:21:12 5 Q Okay. In other words, Vascepa is suitable to reduce
02:21:15 6 triglyceride levels in patients suffering from severe
02:21:19 7 hypertriglyceridemia in less than 12 weeks, right?

02:21:22 8 A Yes.

02:21:22 9 Q And, in fact, some patients with severe
02:21:25 10 hypertriglyceridemia taking icosapent because they don't
02:21:28 11 need to -- let me stop and rephrase.

02:21:30 12 Some patients with severe hypertriglyceridemia
02:21:34 13 stopped taking icosapent because they don't need to take the
02:21:38 14 drug long-term to keep triglycerides below 500, correct?

02:21:41 15 A I think that's a minority, but, yes.

02:21:44 16 Q Okay. And after all, icosapent can significantly reduce
02:21:50 17 triglycerides in as few as four weeks, maybe even sooner,
02:21:55 18 right?

02:21:55 19 A Yeah, I don't think anybody knows sooner, but we have
02:21:58 20 data at four weeks.

02:21:59 21 Q Right. The first data point was four weeks, it could be
02:22:03 22 sooner, we don't know, right?

02:22:04 23 A Yeah, I don't think anybody knows that.

02:22:07 24 Q And let's go to DX 3.26 which is DX 1694, page 214. You
02:22:23 25 recognize this as the MARINE study?

02:22:26 1 A Yes.

02:22:26 2 Q And MARINE reported the most significant reduction in
02:22:30 3 triglyceride levels at just four weeks, right?

02:22:33 4 A Yes.

02:22:33 5 Q And on the screen, just so, you know, everyone is
02:22:36 6 oriented, the baseline median triglyceride was about 680,
02:22:41 7 right?

02:22:41 8 A Yes.

02:22:41 9 Q And then by week four, the median triglyceride dropped to
02:22:47 10 471, right?

02:22:48 11 A Yes.

02:22:48 12 Q And so by week four, the median patient had a
02:22:52 13 triglyceride level below 500, right?

02:22:54 14 A Yes.

02:22:58 15 Q Let's go to the next document which is DX 1816, page 70,
02:23:02 16 and it's DDX 3.27. I will represent to you that this is a
02:23:10 17 document that's already been admitted from Amarin to the FDA.

02:23:17 18 And it says -- this portion of the document says,

02:23:20 19 "Time course of effects: In studies in which
02:23:23 20 serial measurements were performed and/or reported,
02:23:27 21 the maximum effect was seen at four to w 8 weeks,
02:23:31 22 after which time the reduction was maintained."

02:23:34 23 Are you familiar with that?

02:23:36 24 A Yes.

02:23:36 25 Q Okay. And that's an accurate statement, right?

02:23:38 1 A Yes.

02:23:39 2 Q And so icosapent works well if a doctor wants a drug to
02:23:46 3 get triglyceride levels below 500 quickly to eliminate the
02:23:51 4 risk of pancreatitis, right?

02:23:54 5 A To reduce the risk of pancreatitis, yes.

02:23:57 6 Q Fair. Fair point.

02:23:58 7 Okay. So if you assume a patient who has just
02:24:05 8 barely above 500, let's say 510, and the patient can reduce
02:24:10 9 their triglyceride level by 25 percent with diet and exercise
02:24:15 10 eventually, like the -- like the placebo patients in MARINE, a
02:24:20 11 doctor reasonably could prescribe icosapent for short-term use
02:24:24 12 to reduce the pancreatitis risk as soon as possible, right?

02:24:28 13 A So -- yes, they could do that.

02:24:31 14 Q And some of your patients start Vascepa after testing
02:24:36 15 above 500, and then think they don't need the drug anymore
02:24:40 16 once their levels drop below 500, right?

02:24:43 17 A There are some patients who do that, yes.

02:24:46 18 Q In fact, about 5 percent of your patients stopped taking
02:24:51 19 Vascepa after they see their triglycerides drop below 500,
02:24:57 20 right?

02:24:57 21 A Yes.

02:24:58 22 Q And this drop below 500 can happen in less than 12 weeks
02:25:03 23 on icosapent, right?

02:25:05 24 A Theoretically, yes. I don't measure it at less than
02:25:10 25 12 weeks, but, yes.

02:25:11 1 Q Okay. And in your personal practice, some of your
02:25:19 2 patients do take -- strike that.

02:25:23 3 In your -- in your practice, some of your patients
02:25:26 4 with very high triglycerides take Vascepa for less than
02:25:30 5 12 weeks, right?

02:25:31 6 A Yes.

02:25:31 7 Q And when they stop Vascepa, you don't feel that their
02:25:36 8 lives are being put at risk given the pancreatitis risk,
02:25:41 9 right?

02:25:41 10 A The moment they stop? No.

02:25:43 11 Q Okay. And about 5 percent of your patients with severe
02:25:48 12 hypertriglyceridemia take Vascepa for less than 12 weeks,
02:25:51 13 correct?

02:25:51 14 A Yes, for various reasons.

02:25:54 15 Q Now, we've touched on this earlier, but certain drugs can
02:26:02 16 cause triglyceride levels to spike, right?

02:26:05 17 A Yes.

02:26:06 18 Q And we talk about -- we talked about steroids or
02:26:11 19 corticosteroids as an example, right?

02:26:15 20 A Yes.

02:26:15 21 Q And I believe you said corticosteroids can be used short
02:26:19 22 term, right?

02:26:20 23 A They most often are.

02:26:22 24 Q Yeah, less than 12 weeks?

02:26:23 25 A Yes.

02:26:23 1 Q Okay. And a patient who needs a short-term
02:26:26 2 corticosteroid treatment could take Vascepa to counteract the
02:26:30 3 side effect of the triglyceride level spike if necessary to
02:26:33 4 address, right?

02:26:34 5 A Again, a very unusual hypothetical, but I guess that's
02:26:41 6 theoretically possible.

02:26:43 7 Q Now, let's go to DX 2256, page 7, which is DDX 3.28 and
02:26:54 8 you recognize this as the clinical study section of -- this is
02:26:59 9 Hikma's label, but the identical language is in DRL's label,
02:27:05 10 right?

02:27:05 11 A Yes.

02:27:06 12 Q And the clinical study section summarizes the study that
02:27:10 13 justified the FDA approved indication, right?

02:27:14 14 A Yes.

02:27:14 15 Q We know that it's a MARINE study, but the label doesn't
02:27:18 16 actually identify the study name, right?

02:27:20 17 A Correct.

02:27:21 18 Q And the clinical study section provides data beyond the
02:27:27 19 scope of the indication, right?

02:27:27 20 A Yes.

02:27:27 21 Q And some of the data may be relevant to a prescribing
02:27:31 22 physician, right?

02:27:32 23 A Yes.

02:27:32 24 Q But some of the data may be completely irrelevant to a
02:27:36 25 prescribing physician, right?

02:27:38 1 A Yes.

02:27:38 2 Q In other words, some physicians will find some of the
02:27:41 3 clinical study information helpful, but others will find it
02:27:45 4 irrelevant to their practices, right?

02:27:47 5 A Yes.

02:27:47 6 Q And the clinical study section says the study supporting
02:27:53 7 the indication lasted 12 weeks. We talked about earlier,
02:27:56 8 right?

02:27:56 9 A Yes.

02:27:57 10 Q The study certainly didn't last more than a year, right?

02:28:02 11 A That's correct.

02:28:03 12 Q The study ended at 12 weeks, right?

02:28:06 13 A There was the -- the carry-on up to a year.

02:28:10 14 Q For -- right, for some patients.

02:28:12 15 A Yes.

02:28:12 16 Q Okay. And this section -- and we talked about this
02:28:16 17 earlier. This section, the clinical study section, does not
02:28:20 18 specifically instruct doctors that in view of the 12-week
02:28:24 19 clinical study, doctors should go ahead and make sure they
02:28:28 20 give icosapent for at least 12 weeks, right?

02:28:33 21 A Encourages them to use it for at least 12 weeks to see
02:28:37 22 what the effects will be, to see if they achieve the effects
02:28:41 23 in table 2.

02:28:41 24 Q Okay. You're talking about some kind of implied
02:28:44 25 encouragement, right?

02:28:45 1 A I don't want to get into legal terms. I think it
02:28:49 2 encourages physicians to try to follow the clinical study to
02:28:53 3 see if it happens in their patients.

02:28:53 4 Q And just to be clear, I wasn't asking you a legal
02:28:55 5 question. The only time the term 12 weeks is used in
02:28:59 6 defendants' label is to describe the underlying clinical
02:29:02 7 trial, right?

02:29:03 8 A Yes.

02:29:03 9 Q In other words, defendants' labels don't otherwise
02:29:07 10 comment on the 12-week duration such as saying because these
02:29:12 11 effects were achieved in 12 weeks, make sure you give the drug
02:29:17 12 for at least 12 weeks. There's nothing like that, right?

02:29:21 13 A It doesn't say that explicitly, that's correct.

02:29:26 14 Q Let's take a look at the patient information, DX 2256,
02:29:36 15 page 9, which is DDX 3.29. You talked about this on direct,
02:29:41 16 right?

02:29:42 17 A Yes.

02:29:42 18 Q Okay. And the second bullet says,
02:29:45 19 "Do not change your dose or stop taking
02:29:50 20 icosapent ethyl without talking to your doctor,"
02:29:52 21 right?

02:29:52 22 A Yep.

02:29:53 23 Q This statement is it not instructing doctors and patients
02:29:57 24 so use icosapent for at least 12 weeks, right?

02:30:00 25 A Correct.

02:30:01 1 Q In fact, this statement doesn't speak to whether the
02:30:04 2 label is encouraging any particular duration, right?

02:30:07 3 A Right. The statement just warns them if you're going to
02:30:11 4 stop it, talk to your doctor.

02:30:13 5 Q Now, even if one of your patients does not necessarily
02:30:20 6 need icosapent long-term, you still often prescribe it
02:30:25 7 long-term, right?

02:30:26 8 Let me rephrase the question because now there are
02:30:29 9 two indications.

02:30:30 10 Even if your patient with severe
02:30:34 11 hypertriglyceridemia does not necessarily need icosapent long
02:30:39 12 term to address the severe hypertriglyceridemia, you still
02:30:42 13 prescribe the drug long-term, right?

02:30:44 14 A My intent is, when I'm treating people with Vascepa for
02:30:48 15 severe hypertriglyceridemia, that they're going to need the
02:30:50 16 drug long-term, and my intent is to give it to them long-term.

02:30:54 17 Q But you also give your patients Vascepa long-term for
02:30:58 18 reasons unrelated to severe hypertriglyceridemia, right?

02:31:03 19 A Can you say that again? I'm sorry.

02:31:06 20 Q You prescribe Vascepa to your patients for reasons
02:31:10 21 unrelated to controlling severe hypertriglyceridemia.

02:31:13 22 A You're talking about the other indication.

02:31:15 23 Q Right.

02:31:16 24 A I thought we weren't going to talk about the REDUCE-IT
02:31:19 25 indication.

02:31:20 1 Q Well, I'm not going to talk about the specific
02:31:23 2 indication, I'm talking about your practice.

02:31:24 3 A Which addresses the second indication, yes. I use it for
02:31:28 4 the REDUCE-IT indication.

02:31:29 5 Q Okay. And before the new indication was approved, you
02:31:32 6 often prescribed Vascepa for reasons unrelated to controlling
02:31:37 7 severe hypertriglyceridemia, right?

02:31:40 8 A I used it for that same purpose, for the REDUCE-IT type
02:31:43 9 indication, for the REDUCE-IT study results, to try to emulate
02:31:47 10 that in my practice, yes.

02:31:49 11 Q And you also used it because you're not satisfied when
02:31:52 12 your patients have high triglyceride levels. You want it
02:31:56 13 lower, right?

02:31:56 14 A So I would sometimes use it when they were close to 500
02:32:01 15 and not exactly 500, but that would probably be considered an
02:32:05 16 off-label use.

02:32:06 17 Q Right. And before the new indication was approved, you
02:32:09 18 often prescribed Vascepa for off-label uses, right?

02:32:13 19 A Yes.

02:32:14 20 Q And did you do that because you thought that could help
02:32:17 21 address cardiovascular issues, right?

02:32:19 22 A Because I knew the results of REDUCE-IT, the study, I was
02:32:24 23 an investigator, and I wanted to emulate that in my patients.

02:32:27 24 So, yes, there was a window where before REDUCE-IT
02:32:30 25 indication came out, but after the REDUCE-IT trial came out,

1 that I was informed that that's a really good idea to treat
2 those patients to reduce their cardiovascular risk, and I
3 started doing that, and the guidelines encouraged me, but the
4 FDA did not opine on that until December 2019.

5 So there was a window where I was using it for
6 REDUCE-IT, but the indication was not yet in the label.

7 Q Right. And just to be clear, doctors are allowed to
8 prescribe drugs off-label, correct?

9 A Yes.

10 Q So I'm certainly not suggesting you're doing anything
11 wrong. You understand that.

12 A No, I just want to explain why my off-label use.

13 Q Yeah. And so you had patients who had -- who may have
14 presented with triglycerides at, say, 550, who you thought
15 maybe were overweight and weren't in shape and could probably
16 maintain levels below 500 without Vascepa, you told them
17 continue taking the drug because it might have additional
18 benefits, right?

19 A Yeah. Especially after the REDUCE-IT trial, yes.

20 Q Okay. And icosapent is fairly well tolerated, right?

21 A Yes.

22 Q So there's not too much of a downside if your patient is
23 tolerating the medication, and they don't necessarily need it
24 for severe hypertriglyceridemia, to tell them to continue the
25 medication because there may be cardiovascular benefits,

02:33:54 1 right?

02:33:54 2 A That's a given indication now as well, yes.

02:33:57 3 Q Right. And even -- you have -- even before the new
02:34:04 4 indication, you used Vascepa to treat triglyceride levels to
02:34:08 5 get them down as low as 135, right?

02:34:11 6 A I never targeted 135, but some patients might have gotten
02:34:16 7 to 135.

02:34:17 8 135 is the entry criteria for the REDUCE-IT trial.
02:34:22 9 That's not a goal or target. That was -- that just happened
02:34:25 10 to be a random number that was -- that was started at with the
02:34:28 11 study, but the targets are less than 150, not 135.

02:34:33 12 Q I see. But you routinely, before and now after the new
02:34:37 13 indication, have been prescribing Vascepa often to address
02:34:41 14 triglyceride levels that are not above 500 but are still too
02:34:45 15 high, fair?

02:34:46 16 A Yes, the REDUCE-IT indication.

02:34:47 17 Q And you understand that defendants' products will not be
02:34:50 18 indicated for cardiovascular effects, right?

02:34:53 19 A Yes.

02:34:53 20 Q And so even before the new Vascepa indication, about
02:34:57 21 85 percent of your prescriptions were off-label, right?

02:35:01 22 A Again, I just explained why. But, yes, that was the
02:35:04 23 window between the REDUCE-IT results being published and the
02:35:07 24 REDUCE-IT indication being changed by the FDA. At that point
02:35:11 25 I was using it for the REDUCE-IT indication that was not yet

02:35:15 1 part of the label.

02:35:16 2 Q Okay. And just to be more clear, that 85 percent of your
02:35:20 3 patients did not ever have triglycerides above 500, correct?

02:35:24 4 A That -- right, correct.

02:35:26 5 Q Okay. And now that there's a new indication, do you
02:35:29 6 expect the percentage of prescriptions that would be off-label
02:35:36 7 to defendants' labels to be higher than 85 percent?

02:35:41 8 A I think it would be very high. I don't know if it will
02:35:44 9 be higher or lower than 85 percent.

02:35:51 10 MR. KLEIN: Mr. Gross, can you turn to PX 277.

02:35:51 11 BY MR. KLEIN:

02:36:04 12 Q Let's start with the first page. Do you remember this
02:36:06 13 exhibit from the Jacobson reference that you discussed on
02:36:09 14 direct examination?

02:36:10 15 A Yes.

02:36:11 16 Q Okay. I just a couple questions about this.

02:36:14 17 Let's go to page 26, and do you remember discussing
02:36:21 18 this section of the article on follow-up visits?

02:36:26 19 A Yes.

02:36:26 20 Q Okay. And just to be clear, this article in the
02:36:30 21 discussion you were focusing on was talking about statins,
02:36:33 22 right?

02:36:34 23 A This paragraph was talking about statins, yes.

02:36:36 24 Q Right. And if we back out of this and go the page
02:36:40 25 before, which is PX 277, page 25, that section that you were

02:36:49 1 discussing is under a larger header -- heading called
02:36:53 2 Cholesterol Lowering Drug Therapies, right?

02:36:56 3 A Yes.

02:36:57 4 Q Not very high triglycerides, right?

02:37:00 5 A Yes.

02:37:03 6 MR. KLEIN: All right. Let's go back -- can you
02:37:06 7 go back to the PowerPoint.

02:37:06 8 BY MR. KLEIN:

02:37:11 9 Q Let's go back to DDX 3.30. This is again back to the
02:37:16 10 indication. And now you're aware of certain asserted patent
02:37:22 11 claims, and you just discussed them on direct, that focused on
02:37:26 12 lipids other than triglycerides, right?

02:37:28 13 A Yes.

02:37:29 14 Q Now, defendants' labels will be indicated solely to
02:37:31 15 reduce triglycerides in the specific population, right?

02:37:36 16 A Yes.

02:37:36 17 Q And you understand that defendants' labels will not be
02:37:39 18 indicated to reduce any lipid parameter other than
02:37:43 19 triglycerides, right?

02:37:44 20 A Correct.

02:37:45 21 Q And so a doctor could follow the indication in
02:37:47 22 defendants' labels and prescribe their products, once they're
02:37:51 23 introduced, to reduce triglycerides and not focus on any other
02:37:56 24 lipid parameters, right?

02:37:57 25 A They don't have to focus on other parameters, that's

02:38:01 1 correct.

02:38:01 2 Q Let's go to DDX 3.31, we're in DX 2256, pages seven to
02:38:13 3 eight. This is table 2 of defendants' label.

02:38:16 4 I assume this is familiar, right?

02:38:18 5 A Yes.

02:38:19 6 Q And there's a statement underneath the table that you
02:38:23 7 talked about on direct, right?

02:38:24 8 A Yep.

02:38:24 9 Q And that statement is reporting on observations
02:38:30 10 concerning the clinical trial that's being reported in table
02:38:34 11 2, right?

02:38:34 12 A Yes.

02:38:35 13 Q And these are not instructions on how to use icosapent,
02:38:40 14 right?

02:38:40 15 A Correct.

02:38:41 16 Q They're mere descriptions of the clinical study results.

02:38:46 17 A No, they're to show you what to expect if you use the
02:38:49 18 drug.

02:38:49 19 Q Okay. And they're describing the clinical study results,
02:38:53 20 right?

02:38:53 21 A Yes.

02:38:54 22 Q Okay. And, in your opinion, doctors will see the phrase
02:38:59 23 icosapent 4 grams per day, reduce median triglyceride, VLDL-C
02:39:06 24 and apo B levels from baseline relative to placebo and infer
02:39:13 25 an instruction that doctors can expect similar results in a

02:39:16 1 majority of individual patients, right?

02:39:18 2 A Yes.

02:39:18 3 Q And that inference goes beyond the scope of the
02:39:23 4 indication, right?

02:39:24 5 A Of the specific indication? Yes.

02:39:30 6 Q Yes. And median data from a clinical trial may or may
02:39:34 7 not relate to an individual patient depending on, for example,
02:39:37 8 the specific patient population that was being tested, right?

02:39:41 9 A Yes.

02:39:41 10 Q And, for example, the information in the clinical study
02:39:48 11 section says that the median triglyceride level was 684,
02:39:52 12 right?

02:39:53 13 A Yes.

02:39:54 14 Q Okay. And a doctor would understand that the effects
02:39:58 15 listed in table 2 may not be the same if the patient's
02:40:02 16 triglyceride levels were, for example, only 500, right?

02:40:05 17 A As long as they're above 500, they should have these
02:40:09 18 general results.

02:40:10 19 Q Okay. Or a patient with 2,000, with triglycerides of
02:40:13 20 2,000, may or may not receive these -- obtaining those same
02:40:18 21 results, right?

02:40:18 22 A I think patients in this trial with triglycerides above
02:40:21 23 750 did a little better.

02:40:28 24 Q Now, the label, defendants' labels are not encouraging
02:40:32 25 doctors to use Vascepa to obtain effects unrelated to

02:40:37 1 triglycerides, right?

02:40:38 2 A I'm sorry, could you say that again?

02:40:41 3 Q Let me rephrase. Defendants' products are not indicated
02:40:44 4 to control LDL-C, right?

02:40:47 5 A That's correct.

02:40:47 6 Q Okay. And you don't prescribe Vascepa to avoid raising
02:40:51 7 LDL-C, right?

02:40:52 8 A No, that is one of the considerations of why I choose
02:40:55 9 Vascepa over other generics.

02:40:56 10 Q Fair enough. But your intent in prescribing icosapent is
02:41:00 11 to lower triglyceride levels, not to effect LDL-C levels,
02:41:05 12 right?

02:41:05 13 A It's to lower triglyceride levels without raising LDL-C.

02:41:10 14 Q Well, defendants' labels are not encouraging doctors to
02:41:15 15 use the drug because it controls LDL-C, right?

02:41:19 16 A That's correct.

02:41:20 17 Q Let's take another look at table 2 again, it's DX 2256,
02:41:26 18 pages 7 to 8, DDX 3.32, and I want to focus now on the LDL-C
02:41:35 19 results, do you see that?

02:41:36 20 A Yes.

02:41:36 21 Q Now, the doctor would understand from table 2 and the
02:41:40 22 statement below it that we looked at, that there was no LDL-C
02:41:44 23 increase for an average patient, right?

02:41:46 24 A That's true.

02:41:47 25 Q Okay. And there are footnotes that denote the

02:41:50 1 statistical significance, you talked about that, right?

02:41:53 2 A Yes.

02:41:53 3 Q And the LDL-C data does not reference either of the two
02:41:57 4 footnotes, right?

02:41:58 5 A Correct.

02:41:58 6 Q And so a doctor reading defendants' label would
02:42:02 7 understand that the LDL-C data in table 2 is not statistically
02:42:08 8 significant, right?

02:42:09 9 A Correct.

02:42:10 10 Q And there's a column marked Difference (95 Percent
02:42:14 11 Confidence Level), do you see that?

02:42:15 12 A Yes.

02:42:16 13 Q There are two numbers in the parenthesis for the LDL-C,
02:42:21 14 minus 13 and plus eight, right?

02:42:22 15 A Yes.

02:42:23 16 Q And the plus eight means that within the group
02:42:25 17 representing 95 percent of the patients in the study, LDL-C
02:42:30 18 increased as high as eight percent, right?

02:42:32 19 A Yes.

02:42:32 20 Q And that would be a clinically meaningful increase,
02:42:36 21 right?

02:42:36 22 A Yes.

02:42:36 23 Q And the doctor -- so the doctor reading defendants' label
02:42:39 24 would understand that some percentage of patients in this
02:42:43 25 study actually had an LDL-C increase, right?

02:42:46 1 A There will be some, yes. There are outliers to any
02:42:50 2 effect.

02:42:50 3 Q And based on this information in defendants' labels, a
02:42:55 4 doctor would understand that some patients taking icosapent
02:42:59 5 will actually experience a clinically significant LDL-C
02:43:03 6 increase, right?

02:43:04 7 A That is possible, and that's why we repeat the lab values
02:43:08 8 at 12 weeks to see if anything has happened.

02:43:10 9 Q Okay. Let's go to the next slide which is DDX 3.33.
02:43:17 10 We're looking at DX 2256, page 8, which is Hikma's proposed
02:43:23 11 label, and DX 1578 which is the Lovaza label. Both documents
02:43:28 12 are in evidence.

02:43:30 13 You recognize these two documents, right?

02:43:31 14 A Yes.

02:43:32 15 Q And you talked about the Lovaza warning, right?

02:43:36 16 A Yes.

02:43:37 17 Q Okay. And your opinion is that doctors will compare the
02:43:41 18 top snapshot from defendants' labels to the Lovaza warning
02:43:45 19 about LDL-C, right?

02:43:47 20 A Yes.

02:43:49 21 MR. KLEIN: Okay. Actually, it's the Lovaza
02:43:52 22 warning -- that's in evidence, right?

02:43:55 23 Let me move just in case, the Lovaza label may
02:44:00 24 be a PX so let me move to admit DX 1578 just in case it's not
02:44:06 25 in evidence.

02:44:07 1 MR. M. KENNEDY: No objection, Your Honor.

02:44:10 2 THE COURT: It hasn't been admitted. DX 1578 is
02:44:14 3 admitted.

02:44:14 4 (Defendants' Exhibit 1578 received in
02:44:15 evidence.)

02:44:15 5 BY MR. KLEIN:

02:44:16 6 Q And so your opinion with regard to the LDL-C limitation
02:44:22 7 assumes that the doctor reading defendants' label would be
02:44:25 8 aware of this warning in the Lovaza label, right?

02:44:29 9 A Yes.

02:44:30 10 Q And it's your opinion that -- and your opinion assumes
02:44:34 11 that the doctor would compare the adverse reactions from the
02:44:38 12 Lovaza study to the -- Hikma's proposed label and the study in
02:44:46 13 Hikma's label, right?

02:44:48 14 A Yes.

02:44:48 15 Q Okay. And this LDL-C statement in Hikma's label would
02:44:54 16 carry significance to a doctor only because and if the doctor
02:45:00 17 understood that Lovaza had this side effect, right?

02:45:03 18 A Yes.

02:45:04 19 Q Otherwise, it wouldn't mean much to the doctor to say
02:45:08 20 there was no LDL-C increase, right?

02:45:11 21 A Correct.

02:45:13 22 Q Defendants' labels never tell doctors to compare the
02:45:20 23 icosapent clinical trial to the Lovaza clinical trial, right?

02:45:24 24 A Correct.

02:45:25 25 Q And, in fact, defendants' labels don't refer to the

02:45:28 1 Lovaza label at all, right?

02:45:30 2 A Correct.

02:45:31 3 Q Let's go to DDX 3.34 which is DX 2256, page 3. This is
02:45:40 4 section 6.1 of Hikma's propose label. You've seen this,
02:45:44 5 right?

02:45:44 6 A Yes.

02:45:44 7 Q And this section is called Clinical Trials Experience,
02:45:49 8 and it says,

02:45:49 9 "Because clinical trials are conducted under
02:45:52 10 widely varying conditions, adverse reaction rates
02:45:57 11 observed in the clinical trials of a drug cannot be
02:46:01 12 directly compared to rates in the clinical trials of
02:46:05 13 another drug and may not reflect the rates observed
02:46:08 14 in practice," right?

02:46:10 15 A Yes.

02:46:10 16 Q In other words, defendants' labels is telling doctors and
02:46:15 17 warning them against comparing adverse reactions from two
02:46:19 18 clinical trials involving 2 different drugs, right?

02:46:23 19 A Yes.

02:46:29 20 Q So this warning section, 6.1 in defendants' labels, would
02:46:34 21 cover comparing the Vascepa LDL-C adverse reaction rates with
02:46:39 22 the Lovaza LDL-C adverse reaction rates which was obviously a
02:46:45 23 separate trial, right?

02:46:46 24 A Well, the LDL rates are part of the primary study.

02:46:50 25 Adverse reactions are usually side effects like bleeding or

02:46:54 1 joint pain or back pain or rash. So these are a little bit
02:46:59 2 different.

02:46:59 3 Q But a doctor would understand reading -- a doctor reading
02:47:03 4 defendants' labels would understand that two clinical trials
02:47:06 5 involving two different drugs are conducted under different
02:47:10 6 situations, and they may or may not be comparable, right?

02:47:15 7 A Yes.

02:47:16 8 Q And a doctor reading defendants' labels as a whole would
02:47:21 9 obviously see section 6.1, right?

02:47:23 10 A Yes.

02:47:29 11 Q Now, you -- on direct you talked about how some asserted
02:47:35 12 claims require reductions in apo B. Do you remember that?

02:47:39 13 A Yes.

02:47:39 14 Q Let's take another look at Hikma's label DX 2256, page 8,
02:47:48 15 DDX 3.35. And this -- you talked about this statement on
02:47:53 16 direct, "icosapent ethyl 4 grams per day reduced," and I'm
02:47:57 17 just going to focus on "apo B levels from baseline relative to
02:48:03 18 placebo." Do you remember that?

02:48:04 19 A Yes.

02:48:05 20 Q Now, this statement would not necessarily affect
02:48:08 21 prescription decisions, right?

02:48:10 22 A It could because apo B going down would lower
02:48:15 23 cardiovascular risk, and, again, that's an indication for
02:48:17 24 Vascepa.

02:48:17 25 I realize it's not in your label, but we already

02:48:18 1 talked about people potentially using your product off-label
02:48:22 2 to get that benefit. So I think is this the benefit
02:48:25 3 REDUCE-IT, is that Vascepa or icosapent ethyl lowers apo B,
02:48:29 4 therefore lowers cardiovascular risk.

02:48:32 5 So I think this is a very important point that
02:48:34 6 doctors would use the drug for to achieve cardiovascular
02:48:38 7 benefit.

02:48:39 8 Q Okay. And those cardiovascular benefits would be beyond
02:48:43 9 the scope of defendants' labels, right?

02:48:45 10 A Yes.

02:48:46 11 Q Now, on direct you told the Court that you prescribed
02:48:51 12 Vascepa with the intent to reduce apo B; is that right?

02:48:56 13 A Yes.

02:48:56 14 Q But you don't focus on apo B in your practice, right?

02:49:03 15 A I don't often measure it, no.

02:49:06 16 Q You often don't even look at apo B, right?

02:49:11 17 A If it's available, I look at it, but I don't send
02:49:15 18 patients to the lab for apo B measurements routinely.

02:49:15 19 Q And so when you prescribed Vascepa, reducing apo B is not
02:49:21 20 an intended result with regard to treating severe
02:49:25 21 hypertriglyceridemia, right?

02:49:26 22 A No, it's more for cardiovascular risk as I stated.

02:49:32 23 Q And defendants' products are not indicated specifically
02:49:46 24 to reduce triglycerides by any particular amount, right?

02:49:49 25 A That's correct.

02:49:49 1 Q And it would be consistent with the Vascepa labeling to
02:49:53 2 prescribe the drug to patients with severe
02:49:57 3 hypertriglyceridemia even if you only wanted to have a 5
02:50:02 4 percent reduction, right?

02:50:02 5 A I don't think that would be the intent of the physician,
02:50:05 6 but if that occurred, that would still be an on-label use.

02:50:14 7 Q Now, let's take a look at DDX 3.36, and this is DX 2256,
02:50:22 8 page 21. Do you recognize this as claim 1 of the '728 Patent?

02:50:26 9 A Yes.

02:50:27 10 Q And I highlighted the limitation "who does not receive
02:50:31 11 concurrent lipid-altering therapy." Do you see that?

02:50:34 12 A Yes.

02:50:34 13 Q And on direct you testified that a statin is an example
02:50:39 14 of a lipid-altering therapy, right?

02:50:42 15 A Yes.

02:50:42 16 Q Probably the most common example, right?

02:50:44 17 A Yes.

02:50:45 18 Q But there are other lipid-altering therapies, right?

02:50:49 19 A Yes.

02:50:49 20 Q For example, fibrates, niacin, right?

02:50:53 21 A Yes.

02:50:53 22 Q And also Zetia; is that right?

02:50:57 23 A Yes.

02:50:58 24 Q And the chemical name is Ezetimibe?

02:51:03 25 A Yes.

02:51:03 1 Q And in your practice, your patients very commonly take
02:51:08 2 Vascepa with a statin, right?

02:51:10 3 A Yes.

02:51:11 4 Q And you don't read the Vascepa labeling as requiring
02:51:17 5 doctors and yourself to give the drug without a statin, right?

02:51:22 6 A It's -- right. You have the option as a physician to use
02:51:25 7 it with or without a statin.

02:51:28 8 Q For example, you don't -- in your practice, you wouldn't
02:51:31 9 start Vascepa with no statin, wait for the triglycerides to
02:51:38 10 decline below 500, and then add a statin later, right?

02:51:42 11 A I may. I gave an example of that during my direct.

02:51:45 12 Q Okay. But that's not the common way you would use
02:51:48 13 Vascepa, right?

02:51:49 14 A It's more commonly patients are already on a statin and
02:51:53 15 their triglycerides are above 500, so I might implement
02:51:57 16 Vascepa.

02:51:57 17 Q And maintain the statin therapy, right?

02:52:01 18 A Yes.

02:52:01 19 Q And if we go to DDX 3.37, this is DX 2256, page 7, this
02:52:09 20 is the portion of defendants' label that says 25 percent of
02:52:14 21 patients were on concomitant statin therapy, right?

02:52:19 22 A Yes.

02:52:19 23 Q And this is just letting doctors know that 25 percent of
02:52:23 24 patients in the clinical study discussed in the labeling were
02:52:28 25 taking a statin, right?

02:52:29 1 A Yes.

02:52:29 2 Q In other words, this sentence is just -- or this phrase
02:52:34 3 is just discussing the study protocol, right?

02:52:37 4 A Yes.

02:52:38 5 Q This sentence is not an instruction to doctors to make
02:52:42 6 sure they use a statin, right?

02:52:44 7 A It's not a mandate to use a statin in this indication.

02:52:48 8 Q And it's not mandating not to use a statin either.

02:52:51 9 A Right.

02:52:51 10 Q Okay. And this statement doesn't say anything about
02:52:56 11 other lipid-altering therapies, right?

02:52:59 12 A Correct.

02:52:59 13 Q And so the statement is not requiring doctors and
02:53:10 14 patients to take icosapent without any concurrent
02:53:14 15 lipid-altering therapy, right?

02:53:16 16 A It's not forcing them, right. They can use it as
02:53:20 17 monotherapy, it's indicated as monotherapy, but it's not
02:53:24 18 mandated as monotherapy.

02:53:26 19 Q And when you read this phrase, you inferred that
02:53:28 20 75 percent were not on a statin, right?

02:53:31 21 A Yes.

02:53:32 22 Q Okay. But the labeling doesn't say anything about
02:53:35 23 whether this 75 percent of patients were taking a different
02:53:40 24 lipid-altering therapy, right?

02:53:42 25 A Right. We know most of them were not.

02:53:46 1 Q But you know from the MARINE study.

02:53:48 2 A Well, that's what this is referring to, yes.

02:53:50 3 Q No, but if a doctor were just reading the label, the
02:53:54 4 doctor couldn't tell whether those 75 percent of patients were
02:53:57 5 on a different lipid-altering therapy correct?

02:54:01 6 A Right.

02:54:05 7 Q And even if we just focus on statins, there's nothing in
02:54:09 8 the clinical trial section or the label as a whole suggesting
02:54:13 9 any preference for using icosapent with or without a statin,
02:54:17 10 right?

02:54:18 11 A I think it encourages the option of either, but it
02:54:22 12 doesn't say you have to use it one way or the other for that
02:54:26 13 indication.

02:54:27 14 Q And, in fact, a doctor would not even be able to infer a
02:54:32 15 preference with or without a statin from what's in the label,
02:54:36 16 right?

02:54:36 17 A Well, I think, again, it's up to the clinical judgment of
02:54:39 18 the physician and the clinical scenario of patient, and that
02:54:44 19 is left to the doctor, the treating doctor, as we described
02:54:48 20 before.

02:54:48 21 Q Right. So the defendants' labeling leaves it entirely up
02:54:51 22 to the physician's discretion as to whether to add a
02:54:55 23 concurrent lipid-altering therapy to icosapent, correct?

02:55:01 24 A Right. If it's needed you add it, if it's not needed,
02:55:04 25 you don't have to add it.

02:55:04 1 Q All right. Now --

02:55:11 2 THE COURT: Mr. Klein, are you transitioning --

02:55:14 3 MR. KLEIN: I am.

02:55:14 4 THE COURT: -- to another exhibit?

02:55:14 5 I think it would make sense to take our
02:55:16 6 afternoon recess at this time.

02:55:18 7 We'll take a 15-minute recess.

02:55:18 8 (A recess was taken.)

03:16:52 9 THE COURT: Please be seated.

03:16:57 10 Mr. Klein, are you ready?

03:16:59 11 MR. KLEIN: Thank you.

03:16:59 12 BY MR. KLEIN:

03:16:59 13 Q Dr. Budoff, you're not a lawyer, right?

03:17:01 14 A No.

03:17:02 15 Q And you're not an expert in patent law, right?

03:17:06 16 A No.

03:17:06 17 Q And I noticed, for the large part, you avoided any type
03:17:10 18 of legal conclusions, right?

03:17:11 19 A I tried.

03:17:15 20 Q Okay. You're certainly not offering any opinions as to
03:17:19 21 the legal standards for patent infringement, right?

03:17:21 22 A Correct.

03:17:22 23 Q And you're not testifying about whether any language in
03:17:24 24 defendants' proposed labeling actually meets specific legal
03:17:28 25 standards, correct?

03:17:29 1 A Correct.

03:17:29 2 Q You weren't familiar with the legal standards for patent
03:17:34 3 infringement before this case, right?

03:17:36 4 A No.

03:17:36 5 Q And the legal standards for induced infringement can be a
03:17:42 6 bit confusing? Did you find them confusing?

03:17:45 7 A Yes.

03:17:46 8 Q Okay. You're not the only one.

03:17:52 9 But do you understand that you might consider a
03:17:54 10 particular statement in the labeling to encourage
03:17:57 11 infringement, but the case law might require more specific
03:18:01 12 statements to induce, right?

03:18:03 13 A Yes.

03:18:05 14 Q And your understanding when preparing your reports was
03:18:11 15 that a product label induces infringement if the doctor
03:18:15 16 follows the label and ends up using the drug on-label for an
03:18:20 17 infringing use, right?

03:18:21 18 A Yes.

03:18:22 19 Q And on your direct, let's go to DDX 3.38, which is a copy
03:18:29 20 of PDX 2-10, you talked about the legal standards that you
03:18:35 21 applied, right?

03:18:36 22 A Yes.

03:18:36 23 Q And in the second bullet, you said,

03:18:42 24 "Evidence that defendants' labels would
03:18:44 25 inevitably lead some clinicians to infringe

03:18:48 1 establishes defendants' intent to induce
03:18:50 2 infringement," right?

03:18:51 3 A Yes.

03:18:51 4 Q And that came from the lawyers, presumably, right?

03:18:55 5 A Yes.

03:18:56 6 Q And -- but your view in preparing your reports was that
03:18:59 7 at least -- if at least some physicians will prescribe Vascepa
03:19:05 8 or its generic equivalent for severe hypertriglyceridemia to
03:19:09 9 lower triglycerides, that means the label inevitably induces
03:19:14 10 infringement, right?

03:19:15 11 A Yes.

03:19:16 12 Q And you understand that that phrase actually comes from
03:19:19 13 case law?

03:19:20 14 A Yes.

03:19:20 15 Q And you're not offering an opinion on whether that
03:19:25 16 particular phrase as construed by the courts has been
03:19:29 17 satisfied by the labels, right?

03:19:31 18 A Leave that to the Court.

03:19:35 19 Q Exactly.

03:19:36 20 Now, Dr. Budoff, you have a long consulting history
03:19:40 21 with Amarin outside the context of this case, right?

03:19:42 22 A Yes.

03:19:43 23 Q And, for example, Amarin has retained you as a Thought
03:19:47 24 Leader to discuss the Vascepa product?

03:19:48 25 A Yes.

03:19:49 1 Q And you also served on Amarin's Speakers Bureau for
03:19:53 2 Vascepa, right?

03:19:53 3 A Yes.

03:19:54 4 Q Let's go to the next slide, which is DX 2003, and it's
03:20:02 5 DDX 1.39. Did you see this document during opening
03:20:08 6 statements?

03:20:08 7 A Yes.

03:20:09 8 Q Is this a document you've seen before?

03:20:11 9 A No.

03:20:14 10 MR. KLEIN: Okay. I move into evidence DX 2003
03:20:17 11 as an Amarin document.

03:20:21 12 MR. M. KENNEDY: No objection, Your Honor.

03:20:22 13 THE COURT: 2003 is admitted.

03:20:22 14 (Defendants' Exhibit 2003 received in
03:20:28 evidence.)

03:20:28 15 BY MR. KLEIN:

03:20:28 16 Q This -- you were on, and still are, actually, on Amarin's
03:20:32 17 Speakers Bureau, right?

03:20:33 18 A Yes.

03:20:36 19 Q Okay. And this -- this document says, "Dear VITAL
03:20:43 20 Speakers." Do you understand VITAL is an abbreviation for
03:20:47 21 advanced -- to Advance Interventions and Total Assessment of
03:20:51 22 lipids?

03:20:51 23 A Yes.

03:20:52 24 Q Do you know what that is?

03:20:53 25 A That's just the name of their Speakers Bureau.

03:20:57 1 Q I see. Okay.

03:20:59 2 And that's -- the Dr. Matthew Budoff is you on this
03:21:01 3 page, right?

03:21:02 4 A Yes.

03:21:02 5 Q And you recognize Dr. Toth as well?

03:21:04 6 A Yes.

03:21:05 7 Q And you recognize Dr. Mason?

03:21:08 8 A Yes.

03:21:08 9 Q Do you understand he, along with yourself and Dr. Toth,
03:21:12 10 are all experts for Amarin in this case?

03:21:14 11 A Yes.

03:21:16 12 Q And if we go to DDX 3.40, there's a picture of Dr.
03:21:26 13 Miller, right?

03:21:26 14 A Yes.

03:21:27 15 Q Is that the doctor who wrote the publication we looked at
03:21:32 16 earlier?

03:21:33 17 A Yes.

03:21:33 18 Q Okay. And you understand now that he was actually
03:21:35 19 retained as another Amarin expert earlier in the case?

03:21:38 20 A You told me that, yes.

03:21:39 21 Q Yeah.

03:21:40 22 And you began consulting for Amarin about eight
03:21:43 23 years ago, in 2012?

03:21:46 24 A Yeah. I'd have -- I don't know exactly, but somewhere
03:21:49 25 around that time.

03:21:50 1 Q Okay. And with regard to Amarin's Speakers Bureau, you
03:21:54 2 encourage clinicians to use Vascepa, right?

03:21:57 3 A No, I try to educate them on the science and the
03:22:01 4 guidelines. It's not my job, nor would I ever encourage them
03:22:05 5 to use a specific product outside of what would be appropriate
03:22:09 6 and best for the patient's care.

03:22:11 7 Q Okay. Understood. But Amarin was paying you to go out
03:22:15 8 and speak to doctors about Vascepa, right?

03:22:17 9 A Yes. I get paid by a lot of different groups to give
03:22:22 10 lectures. It's on my own time. I have to travel. So I do
03:22:26 11 get compensated when I have to lecture most of the time.

03:22:30 12 Q You served as an Amarin speaker for Vascepa about a 100
03:22:34 13 times; is that right?

03:22:35 14 A I wouldn't know exactly, but it's possible over the seven
03:22:39 15 years.

03:22:40 16 Q You estimate maybe 100 in your deposition. Does that
03:22:45 17 sound right?

03:22:45 18 A Yeah.

03:22:45 19 Q And I think you've said this earlier, you're still a
03:22:49 20 speaker for Vascepa today, right?

03:22:50 21 A Yes.

03:22:51 22 Q And as an Amarin Thought Leader, you gave Amarin advice
03:22:55 23 on how to help market Vascepa to physicians, right?

03:22:58 24 A Not generally. I usually give them advice on what
03:23:02 25 science to do or what next study to do.

03:23:05 1 I've met with them about the EVAPORATE trial and
03:23:08 2 tried to encourage them to do other studies. I'm not a
03:23:12 3 marketing expert, so I don't give them marketing advice.

03:23:14 4 Q You gave Amarin general advice or direction on what
03:23:17 5 things about Amarin's clinical study may resonate with
03:23:21 6 clinicians or what things should be emphasized or
03:23:25 7 de-emphasized; is this right?

03:23:26 8 A Yes.

03:23:26 9 Q And you also consulted with Amarin on the REDUCE-IT
03:23:29 10 trial? You talked about that, right?

03:23:31 11 A Yeah. I wasn't directly involved in the REDUCE-IT trial,
03:23:34 12 outside of being a principal investigator. I wasn't on the
03:23:37 13 steering committee or anything. So, I wasn't really involved
03:23:40 14 in that other than recruiting some patients locally at my own
03:23:44 15 site.

03:23:45 16 Q Okay. And just to be clear, REDUCE-IT focused on a
03:23:45 17 different patient population than the patient population we're
03:23:50 18 talking about in defendants' labels, right?

03:23:50 19 A Yes.

03:23:50 20 Q And you also sent proposals to Amarin with regard to the
03:23:55 21 EVAPORATE trial, right?

03:23:57 22 A Yes.

03:23:57 23 Q And since 2016, about half of your income comes from
03:24:05 24 pharmaceutical companies, including Amarin, right?

03:24:09 25 A All lectures combined, but, yes.

03:24:12 1 Q And about 10 percent of your income comes from Amarin,
03:24:15 2 right?

03:24:15 3 A Yeah.

03:24:17 4 Q And you also testified for Amarin at the FDA Advisory
03:24:21 5 Committee meeting held last November for the new REDUCE-IT
03:24:25 6 indication, right?

03:24:26 7 A I was just a public speaker. That was on my own behalf.

03:24:30 8 MR. KLEIN: Okay. Let's go to DX 2246, pages 1
03:24:36 9 and 62, and it's DDX 3.41. This is Amarin's supplemental NDA
03:24:44 10 financial disclosure.

03:24:49 11 We'll move this into evidence.

03:24:51 12 MR. M. KENNEDY: No objection, Your Honor.

03:24:52 13 THE COURT: 2246 is admitted.

03:24:52 14 (Defendants' Exhibit 2246 received in
03:24:55 evidence.)

03:24:55 15 BY MR. KLEIN:

03:24:56 16 Q I don't know, have you seen Amarin's financial disclosure
03:24:59 17 with regard to its supplemental NDA?

03:25:02 18 A No.

03:25:02 19 Q Okay. I'll represent to you that that's what this is.

03:25:05 20 You know what the financial disclosure is, right?

03:25:07 21 A Yes.

03:25:08 22 Q And Amarin had to make financial disclosures to the FDA
03:25:13 23 for you and other investigators, right?

03:25:16 24 A Yes.

03:25:17 25 Q Okay. And Amarin submitted this document on March -- in

03:25:23 1 March 2019, right? You see that at the bottom?

03:25:26 2 A Yes.

03:25:27 3 Q Okay. If we turn to Section 3, it's DX 2246, page 3,
03:25:34 4 DDX 3.42, the document -- you see the title, Clinical
03:25:40 5 Investigators With Disclosable Interests?

03:25:43 6 A Yes.

03:25:44 7 Q And the document explains that,

03:25:45 8 "Clinical investigators with disclosable
03:25:47 9 financial interests including a significant equity
03:25:52 10 interest in the sponsor of the covered study as
03:25:55 11 defined in" the regulations "and/or significant
03:25:59 12 payments of other sorts (SPOOS)," S-P-O-O-S, "as
03:26:04 13 defined" in the regulations, "are provided in Table
03:26:08 14 1. Details of their disclosed financial interests
03:26:11 15 and arrangements are included in Table 2."

03:26:14 16 Do you see that?

03:26:15 17 A Yes.

03:26:16 18 Q All right. Now, let's go to the next slide DX 2246,
03:26:22 19 pages 3 to 4. This is DDX 3.43. You see this is Table 1?

03:26:30 20 A Yes.

03:26:30 21 Q And can you see that you are one of the doctors who was
03:26:35 22 disclosed by Amarin?

03:26:37 23 A Yes.

03:26:37 24 Q And if my count's right, there were 12 in total.

03:26:41 25 A Okay.

03:26:41 1 Q All right. Now, turning to the next page, DX 2246,
03:26:46 2 page 7, this is DDX 3.44, Table 2 lists the details of the
03:26:54 3 disclosed financial interests and arrangements for the 12
03:26:57 4 people we just looked at. Do you understand that?

03:26:59 5 A Yes.

03:27:00 6 Q Okay. And, again, this -- you are the Matthew Budoff on
03:27:04 7 the left there?

03:27:05 8 A Yes.

03:27:06 9 Q And Table 2 lists SPOOS, which was defined earlier as
03:27:13 10 Significant Payments of Other Source -- Sorts, for you of
03:27:18 11 close to \$1.3 million. Do you see that?

03:27:20 12 A Yes.

03:27:21 13 Q And then the table breaks this down. Do you see that?

03:27:24 14 A Yes.

03:27:25 15 Q And so Amarin has provided you with a research grant of
03:27:30 16 \$900,000 related to the EVAPORATE study, right?

03:27:34 17 A That goes to my institution, not to me, but, yes.

03:27:37 18 Q And just so you know, my next question was, to be fair,
03:27:39 19 you didn't receive the money personally.

03:27:41 20 A Right.

03:27:42 21 Q Okay. But it does help a study that you proposed to
03:27:45 22 Amarin, right?

03:27:46 23 A Yes.

03:27:46 24 Q And you're the principal investigator for that study.

03:27:50 25 A Yes.

03:27:50 1 Q And your name will be associated with the results of the
03:27:54 2 study if it's successful, right?

03:27:56 3 A It already is. I've been publishing on that trial.

03:27:59 4 Q We go to the next slide, it's the same page, different
03:28:02 5 highlighting, DDX 3.45, you received a higher research grant
03:28:08 6 than any of the other 11 individuals listed in the table,
03:28:11 7 right?

03:28:12 8 A Yes.

03:28:12 9 Q Now, if we go to the next slide, which is DDX 3.46,
03:28:20 10 again, it's the same slide, I just changed the highlighting.
03:28:25 11 If we take out the \$900,000 grant, the rest of the
03:28:31 12 \$1.3 million was paid by Amarin to you personally, right?

03:28:35 13 A No. The honorarium and consulting fees goes to me
03:28:40 14 personally. A lot of the compensation might go to my
03:28:44 15 institution. For example, I do educational programs at my
03:28:47 16 institution, and they support that. That money would go to
03:28:52 17 the institution and not to me.

03:28:53 18 Q Okay. But it's your institution, correct?

03:28:57 19 A No, I don't own it. It's named the Lundquist Institute.
03:29:01 20 I'm one of 1,000 investigators there, and the money that goes
03:29:07 21 to the institute supports all of our services there; research,
03:29:11 22 pharmacies, the statistics, a lot of different things.

03:29:15 23 Q Okay.

03:29:16 24 A It doesn't benefit me personally in any way.

03:29:19 25 Q Well, it benefits you personally indirectly to the extent

03:29:24 1 it's benefitting an institution to which you belong, correct?

03:29:27 2 A Well, yes, but they just received a \$70 million grant to
03:29:31 3 name the institution, so my contribution of a total of 300,000
03:29:35 4 is probably not very significant, and that money doesn't go to
03:29:39 5 me as well.

03:29:40 6 So I would say that I'm definitely responsible for
03:29:42 7 receiving the consulting fees of 33,000 and the honorarium of
03:29:47 8 27,000. I don't know what education of \$42 represents, but
03:29:51 9 let's -- I'll take credit for that as well, maybe I received
03:29:55 10 that payment.

03:29:55 11 Q Okay. Over the years, for your consulting work,
03:30:00 12 unrelated to this case, you would guess you have received
03:30:07 13 probably \$300,000, or something over, spanning the last eight
03:30:10 14 years, right?

03:30:11 15 A No, nowhere near that number.

03:30:13 16 Q Okay.

03:30:14 17 A That would be listed here if that were the case.

03:30:17 18 MR. KLEIN: Mr. Gross, can you play the 272 --
03:30:20 19 page 272 of his deposition, line 24, to 273, line 6.

03:30:51 20 (Deposition video played.)

03:30:52 21 BY MR. KLEIN:

03:30:53 22 Q Doctor, was that your testimony?

03:30:54 23 A Yes, but that includes money that goes to my institution,
03:30:57 24 not to me personally.

03:30:58 25 Q The question -- okay.

03:30:59 1 A I apologize. I didn't understand your question.

03:31:02 2 Yes. It says right here, 302,000. I think that
03:31:05 3 number is probably very accurate.

03:31:08 4 MR KLEIN: No further questions.

03:31:12 5 MR. M. KENNEDY: Your Honor, I do have a little
03:31:14 6 bit of redirect.

03:31:22 7 Your Honor, may I proceed?

03:31:24 8 THE COURT: Yes.

03:31:25 9 REDIRECT EXAMINATION

03:31:25 10 BY MR. KENNEDY:

03:31:25 11 Q So, Dr. Budoff, I'm going to jump around a few topics you
03:31:30 12 covered with Mr. Klein just now.

03:31:31 13 Mr. Klein asked you about whether Vascepa was
03:31:34 14 suitable to reduce triglycerides in severely
03:31:37 15 hypertriglyceridemic patients in less than 12 weeks.

03:31:42 16 Do you remember that discussion?

03:31:43 17 A Yes.

03:31:43 18 Q And you do you remember the related discussion with
03:31:45 19 Mr. Klein about whether triglyceride levels are reduced in
03:31:50 20 less than 12 weeks? Do you remember that testimony?

03:31:53 21 A Yes.

03:31:53 22 Q Now, once a severely hypertriglyceridemic patient's
03:31:57 23 triglyceride levels have been reduced, is therapy complete?

03:32:01 24 A No.

03:32:02 25 Q Why not?

03:32:03 1 A Well, again, if you stop the therapy, in most cases it
03:32:08 2 will go back up. We've seen that in the MARINE trial. We see
03:32:12 3 that in clinical practice, that in a vast majority of patients
03:32:16 4 triglycerides will not say below 500 without additional
03:32:20 5 medical therapy.

03:32:21 6 Q What is the therapeutic goal for a patient with severe
03:32:25 7 hypertriglyceridemia?

03:32:26 8 A The goals and the guidelines are to reduce and maintain
03:32:30 9 their triglycerides below 500 milligrams per deciliter.

03:32:33 10 Q Now, for a severely hypertriglyceridemic patient who
03:32:38 11 doesn't have what we've been calling one of the reversible
03:32:40 12 causes of severe hypertriglyceridemia, how do you maintain a
03:32:43 13 reduction in triglyceride levels?

03:32:45 14 A So in almost all cases I continue the therapy long-term,
03:32:49 15 as I've described this morning and this afternoon.

03:32:52 16 Q With your typical patients who have very high
03:32:56 17 triglycerides or severe hypertriglyceridemia, would you know
03:32:59 18 if they had reduced their triglycerides below 500 in fewer
03:33:03 19 than 12 weeks?

03:33:04 20 A No. I don't usually bring them in for lab testing at a
03:33:09 21 shorter interval.

03:33:10 22 Q Do you know of any clinicians who do, as a habit?

03:33:13 23 A No. I think the vast majority, if not all physicians
03:33:17 24 that I'm aware of, their practice patterns revolve around what
03:33:21 25 we would call a typical practice, and a typical practice would

03:33:24 1 be to repeat the results at three months, to bring them back
03:33:27 2 at three months for a follow-up visit.

03:33:29 3 Q Now, Mr. Klein also asked you on cross about whether your
03:33:32 4 patients ever take Vascepa for less than 12 weeks.

03:33:37 5 Do you remember that testimony?

03:33:37 6 A Yes.

03:33:38 7 Q And I think you said that some of your patients do take
03:33:40 8 Vascepa for less than 12 weeks. Do you remember that?

03:33:42 9 A Yes.

03:33:43 10 Q Now, have you ever prescribed Vascepa to a patient with
03:33:47 11 severe hypertriglyceridemia for fewer than 12 weeks?

03:33:51 12 A No. The shortest prescription I've ever written would be
03:33:54 13 a one month prescription with three refills. So that would be
03:33:58 14 four months, at a minimum, to get them to the three-month
03:34:02 15 follow-up, where I can reassess their lipids.

03:34:05 16 Q So I think you alluded to some reasons why one of your
03:34:08 17 patients might, nonetheless, take Vascepa for fewer than 12
03:34:12 18 weeks. Can you explain what those reasons are.

03:34:14 19 A Yeah. So most commonly they go to the pharmacy, and the
03:34:17 20 price is too high, and they say, "I can't afford it," and so
03:34:20 21 they don't want to take it, and they call me and they say,
03:34:24 22 "Can I take something else?"

03:34:25 23 Second most commonly would be side effects.
03:34:28 24 Patients perceive side effects, even though Vascepa I consider
03:34:33 25 generally safe. I would say that Vascepa is -- has some side

03:34:40 1 effects and some issues with tolerability. So some people
03:34:45 2 would say, "Oh, I feel joint aches," or, "I'm getting some
03:34:49 3 other problem. I'm going to stop the therapy before 12
03:34:49 4 weeks."

03:34:52 5 Q Now, you had a discussion with Mr. Klein about whether
03:34:55 6 there are patients with very high triglycerides who can have
03:34:59 7 their condition addressed solely with diet and lifestyle.

03:35:03 8 Do you remember that discussion?

03:35:04 9 A Yes.

03:35:05 10 MR. M. KENNEDY: Mr. Brooks, can we have PX 989.
03:35:08 11 This is ATP III guidelines we a looked at earlier today.

03:35:13 12 COMPUTER TECHNICIAN: Madam clerk, can you
03:35:15 13 switch me?

03:35:21 14 MR. M. KENNEDY: And, Mr. Brooks, if you'd go to
03:35:23 15 page 195 of the document and blowup the left-hand column.

03:35:23 16 BY MR. M. KENNEDY:

03:35:28 17 Q So, Dr. Budoff, do you recognize this passage?

03:35:31 18 A Yes.

03:35:31 19 Q I think we discussed portions of this earlier today.

03:35:34 20 A Yes.

03:35:35 21 Q I would like to direct you a few lines down, and the
03:35:38 22 heading of this passage is Very High Triglycerides. What is
03:35:41 23 your understanding of why this passage is headed that way?

03:35:45 24 A This is the part of the document that addresses severe
03:35:51 25 hypertriglyceridemia.

03:35:52 1 MR. M. KENNEDY: So, Mr. Brooks, I would like to
03:35:54 2 go about ten lines down and highlight the sentences beginning
03:35:58 3 with "weight reduction and increased physical activity," and
03:36:01 4 go through the word "pancreatitis," about five lines down.

03:36:01 5 BY MR. M. KENNEDY:

03:36:08 6 Q And, Dr. Budoff, if you could review this passage and let
03:36:12 7 me know what, if anything, does this passage tell you about
03:36:15 8 the clinical needs of patients with severe
03:36:18 9 hypertriglyceridemia?

03:36:20 10 A Well, it's just saying that after lifestyle modifications
03:36:24 11 are emphasized, triglyceride-lowering drugs are usually
03:36:28 12 required. So, it just tells you that most patients -- as we
03:36:33 13 discussed this afternoon, most patients fail diet and exercise
03:36:37 14 as a primary treatment strategy.

03:36:40 15 Q And what if a patient succeeds with diet and lifestyle
03:36:45 16 changes?

03:36:45 17 A Well, if they were successful, then they would not be
03:36:48 18 indicated to start Vascepa, and I would just continue
03:36:51 19 lifestyle changes, as least for the MARINE indication purposes
03:36:54 20 of discussion.

03:36:56 21 Q So you also had some discussion with Mr. Klein about
03:36:59 22 LDL-C. Do you remember that testimony?

03:37:01 23 A Yes.

03:37:01 24 Q What would a clinician in your field know about LDL-C,
03:37:07 25 just whether it's good or bad, what its function is?

03:37:11 1 A I would hope that every person who is practicing in the
03:37:18 2 field of lipids understands that LDL cholesterol is bad.

03:37:22 3 Q And they would understand that, all things being equal,
03:37:25 4 it would be better to have low LDL-C rather than high LDL-C?

03:37:32 5 A Yes.

03:37:32 6 Q Is this knowledge that clinicians in your field would
03:37:34 7 have in their minds when reviewing the Vascepa labeling and
03:37:36 8 particularly the clinical data?

03:37:38 9 A Yes.

03:37:38 10 Q Is this background knowledge -- would that affect your
03:37:42 11 treatment decisions for patients with severe
03:37:46 12 hypertriglyceridemia?

03:37:46 13 A That would really be the only reason, short of the
03:37:50 14 REDUCE-IT indication, to use Vascepa preferentially over the
03:37:54 15 less expensive fibrates or Lovaza which has a generic
03:37:59 16 alternative.

03:37:59 17 So, we go through great steps to get patients on
03:38:02 18 Vascepa right now. I have to often call the insurance
03:38:06 19 company. I have to convince them that my patient meets the
03:38:09 20 criteria. I have to then sometimes get a formal prior
03:38:13 21 authorization approved.

03:38:14 22 So I go through steps. The patient has to pay extra
03:38:17 23 money at the pharmacy, all of that. The primary reason is not
03:38:21 24 because it's the best triglyceride-lowering drug, but because
03:38:26 25 it's the best drug at not -- that lowering triglycerides will

not affect that LDL cholesterol.

So, I think that becomes paramount in the clinician's decision to use Vascepa over generic alternatives.

Q So just to be clear, these considerations that you just mentioned, do they affect your decision about which medication to prescribe with patients with severe hypertriglyceridemia?

A Absolutely.

Q So Mr. Klein asked you some questions about the clinical effects experienced by patients who take Vascepa, and particularly whether some patients may not achieve the clinical effects touted in the clinical trial section of the label. Do you remember that testimony?

A Yes.

Q Now, when you administer Vascepa to a patient by writing a prescription, and a patient with severe hypertriglyceridemia, what clinical effects do you expect to achieve at the moment you write that prescription?

A So my intent is that they will follow the general results of the MARINE trial, that they will get a triglyceride reduction of about a third, that their LDL cholesterol will not go up, that their apo B will go down.

Obviously there are patient-to-patient differences. That's why I have to retest them at 12 weeks to see what really happened in my patient.

Q So what percentage of your patients end up achieving the

03:39:44 1 effects touted in Table 2 of the labeling, that is, severely
03:39:49 2 hypertriglyceridemic patients to whom you prescribe Vascepa
03:39:54 3 according to the labeling?

03:39:55 4 A Yeah. So we know it's about three-quarters of patients
03:39:58 5 will achieve that general result, and there will be some
03:40:01 6 people on the outsides of that, the extremes.

03:40:04 7 Q I think you called them outliers in your discussion with
03:40:06 8 Mr. Klein?

03:40:07 9 A Yes.

03:40:08 10 Q So at the moment you write the prescription to a patient
03:40:13 11 with very high triglycerides, do you have any way of knowing
03:40:15 12 whether that patient is going to be an outlier?

03:40:18 13 A No.

03:40:18 14 Q So, I would like to ask you couple questions about apo B.
03:40:24 15 So am I -- is treating very high triglycerides with
03:40:28 16 Vascepa in order to reduce triglycerides and lower apo B, is
03:40:32 17 that on-label?

03:40:35 18 A Yes.

03:40:36 19 Q Is that part of your prescribing practice to patients
03:40:40 20 with very high triglycerides?

03:40:42 21 A Yes.

03:40:42 22 Q And, finally, I would like to go to a document that
03:40:49 23 Mr. Klein used with you, it's your reply expert report, and
03:40:52 24 this is PX 177.

03:40:58 25 MR. M. KENNEDY: And, Mr. Brooks, if you could

1 turn to page 23 of this document.

2 BY MR. M. KENNEDY:

3 Q Now, Mr. Klein showed you paragraph 54 of your expert
4 report, and 57, but I would like to show you a couple
5 surrounding paragraphs that he didn't show you, and starting
6 with paragraph 53.

7 MR. M. KENNEDY: And, Mr. Brooks, can you blow
8 that up, please. And maybe put 53 along with 54, if you're
9 able to do that.

10 BY MR. M. KENNEDY:

11 Q Now, Dr. Budoff, again, Mr. Klein showed you 54. He
12 didn't show you 53. Could you just review 53 and then tell us
13 what was the context in which you were giving the opinions
14 that Mr. Klein showed you in 54?

15 A (Witness reviews document.)

16 Yeah. So this is suggesting that even though
17 Dr. Sheinberg has given them the medication, that he's
18 instructed them to wait six weeks before filling the
19 prescription and then coming back at 12 weeks. Therefore,
20 when they return, they've only received six weeks of therapy
21 and not 12 weeks of therapy.

22 Q Do you agree with Dr. Sheinberg's theory as stated in
23 paragraph 53?

24 A This has, to my knowledge, never been practiced this way,
25 and this would not be how any physician that I've ever

encountered would prescribe medication.

We give them the prescription and say start this medicine. And if we don't want them to start the medicine, we wouldn't give them the prescription.

I don't give them a prescription and say put in your calendar for six weeks from now to go to the pharmacy and fill this. That would not work in clinical practice, and it's not recommended approach to treatment.

Q Now, at the time you wrote this reply expert report, you gave a number of reasons why you disagree with Dr. Sheinberg; is that right?

A Yes.

Q And Mr. Klein did show you a couple of those reasons in paragraphs 54 and 57; is that right?

A Yes.

Q Now, he didn't show you paragraph 55, which Mr. Brooks has kindly put on the screen. And I'll read it into the record.

"To begin with, the Prescribing Information counsels that the drug should be given to patients for whom efforts to reduce their triglycerides below 500 milligrams per deciliter, using only diet and lifestyle modifications, have been unsuccessful."

Do you see that?

A Yes.

03:43:26 1 Q Now, you reference the Prescribing Information. Are
03:43:29 2 there particular portions of the Prescribing Information that
03:43:32 3 counsel that drug should only be given to patients who can't
03:43:36 4 reduce their triglycerides below 500 without -- through just
03:43:40 5 diet and lifestyle?

03:43:42 6 A Yes.

03:43:42 7 Q Which portions do you have in mind?

03:43:45 8 A Well, we talked about Section 2, the dosing and
03:43:48 9 administration. I think that explicitly states that you
03:43:52 10 should use diet and lifestyle. The patient should engage in
03:43:55 11 diet and lifestyle before using therapy, and then, obviously,
03:43:58 12 if they're still not at goal, you would put them on therapy.

03:44:02 13 Also, the Section 14, the clinical trial section, we
03:44:06 14 know and we reviewed that this afternoon as well, the MARINE
03:44:10 15 trial was done with that six- to nine-week washout period
03:44:14 16 where they documented that after diet and lifestyle failed, if
03:44:18 17 their triglycerides were still above 500, were then they
03:44:23 18 enrolled in the study.

03:44:24 19 Q Now, people who are able to reduce their triglycerides
03:44:28 20 below 500 with diet and lifestyle, is Vascepa indicated for
03:44:32 21 those patients?

03:44:33 22 A Well, now it is. The REDUCE-IT indication may play a
03:44:37 23 role depending on their underlying cardiovascular risk. But
03:44:41 24 for severe hypertriglyceridemia, the MARINE indication, it
03:44:44 25 would not be indicated.

03:44:48 1 MR. M. KENNEDY: Your Honor, I have no further
03:44:50 2 questions.

03:44:50 3 THE COURT: Mr. Klein?

03:44:51 4 MR KLEIN: No further questions.

03:44:52 5 THE COURT: All right. Thank you, Dr. Budoff.
03:44:54 6 You may step down.

03:44:54 7 THE WITNESS: Thank you very much.

03:44:56 8 MR. SIPES: Your Honor, Christopher Sipes for
03:45:03 9 Amarin. With that, plaintiffs close their opening case.

03:45:07 10 MR KLEIN: Your Honor, Ms. Fundakowski is going
03:45:11 11 to address the fact that plaintiffs have closed their case,
03:45:14 12 and Ms. Fundakowski will make a motion.

03:45:32 13 MS. FUNDAKOWSKI: Claire Fundakowski on behalf
03:45:36 14 of the defendants Hikma.

03:45:38 15 Your Honor, we understand that this is a bench
03:45:41 16 trial, but if Your Honor is so inclined, defendants would like
03:45:45 17 to move for a judgment on partial findings under Rule 52(c).

03:45:49 18 Plaintiff's sole infringement theory is that
03:45:52 19 defendants --

03:45:52 20 THE COURT: Now, you need -- I don't know if
03:45:53 21 you're reading from something. You need to slow down if you
03:45:57 22 are reading because, otherwise, the court reporter will remind
03:46:00 23 you to slow down. I also want to take some notes, so you need
03:46:03 24 to indulge me.

03:46:06 25 MS. FUNDAKOWSKI: Thank you, Your Honor.

Plaintiff's sole infringement theory is that defendants' proposed labels will actively induce doctors to infringe the claims. To prevail, plaintiff's must show by preponderance of the evidence that defendants have the specific intent, based on the contents of their proposed labels, to encourage physicians to prescribe defendants' ANDA products in an infringing manner. Plaintiffs have failed to meet this burden.

Among other limitations, each of the asserted claims requires at least 12 weeks of treatment. As recognized in the Court's summary judgment order and confirmed by today's testimony, defendants' proposed labels do not explicitly tell doctors they should prescribe the drug for at least 12 weeks.

Plaintiffs therefore argue that the Court should infer that defendants induce infringement because defendants' proposed labels instruct doctors to treat severe hypertriglyceridemia as an adjunct to diet.

Plaintiffs' evidence fails to show that defendants' proposed labels induce physicians to prescribe icosapent for at least 12 weeks.

Under *Grunenthal*, 919 F.3d 1333 at 1339, even if the indicated use includes the patented use, there is no inducement if the proposed labels do not specifically encourage the patented use.

The rationale for the Federal Circuit's

03:47:43 1 *Grunenthal* decision is rooted in plaintiff's burden to prove
03:47:47 2 that defendants possessed specific intent to induce
03:47:50 3 infringement.

03:47:51 4 Because the plaintiff in that case could not
03:47:53 5 show that the indicated use was coextensive with or required
03:48:00 6 the patented use, the Court could not infer that defendants
03:48:04 7 had a specific intent to induce infringement.

03:48:08 8 The Federal Circuit reached this conclusion in
03:48:12 9 *Grunenthal* even though plaintiff presented evidence that, I
03:48:14 10 quote, "most of the uses of their proposed ANDA products would
03:48:19 11 be directed to," end quote, the claimed use. And that was at
03:48:24 12 1340.

03:48:25 13 Here, for the same reason, plaintiffs have
03:48:28 14 failed to show that defendants' proposed labels will induce
03:48:32 15 prescribers to treat patients for at least 12 weeks. The
03:48:35 16 undisputed evidence that defendant proposed -- show that the
03:48:41 17 defendants' proposed labels are indicated for conditions that
03:48:44 18 do not require treatment --

03:48:45 19 THE COURT: Where is the undisputed evidence?

03:48:48 20 MS. FUNDAKOWSI: I believe we heard Dr. Budoff
03:48:51 21 testify today that severe hypertriglyceridemia has, I quote,
03:48:54 22 reversible causes, which according to Dr. Budoff would, I
03:48:58 23 quote, not be considered a chronic condition.

03:49:02 24 Dr. Budoff agreed with plaintiffs' invalidity
03:49:05 25 expert, Dr. Toth, that severe hypertriglyceridemia, I quote,

1 can be acute -- an acute phenomenon.

2 Dr. Budoff testified that weight loss of 5
3 percent to 10 percent can result in a 20 percent decrease in
4 triglycerides. He testified that it is possible to see
5 reductions in triglycerides of up to 50 percent without any
6 medication.

7 And even in the MARINE study, in the patient
8 population that received four to six weeks of diet and
9 exercise, they were unable to reduce their triglycerides.
10 Dr. Budoff testified, and as shown in DX 1701-51, that about
11 21 percent of patients falling within the scope of defendants'
12 proposed indication can reduce and maintain their
13 triglycerides down to below 500 milligrams per deciliter with
14 diet and exercise alone, or, in other words, without the need
15 for continued drug treatment for at least 12 weeks.

16 Plaintiffs' evidence therefore fails to show
17 that the Court can infer that defendants' proposed labels
18 induce doctors to prescribe icosapent for a period of at least
19 12 weeks.

20 Plaintiffs argue that specific intent to induce
21 infringement can be inferred because, according to plaintiffs,
22 defendants' proposed labels would inevitably lead some
23 physicians to prescribe icosapent for at least 12 weeks, but
24 plaintiff's misstate the legal standard.

25 The Federal Circuit has never held that

1 inducement can be inferred if only some physicians will
2 eventually infringe. Rather, the law merely holds that an
3 instruction to infringe need not be directed to all physicians
4 in order for there to be inducement.

5 This case law does not apply here because there
6 is no such instruction inducing infringement. For example, in
7 *Eli Lilly*, 845 F.3d 1357 at 1369, the Court found that
8 repeated instructions and warnings throughout defendants'
9 proposed labeling demonstrated specific intent to induce
10 infringement.

11 As explained at 1368, the Court explained that
12 the instructions teach an infringing use such that we are
13 willing to infer from those instructions an infirmative intent
14 to infringe the patent.

15 The Federal Circuit there did not require
16 evidence that all physicians would follow those repeated
17 instructions and warnings, but in light of the unambiguous,
18 repeated instructions and warnings, the Court explained at
19 1369 that it was sufficient that those instructions, I quote,
20 would inevitably lead some physicians to infringe.

21 Likewise in *Vanda*, 887 F.3d 1117 at 1131, the
22 court found that there was a recommendation to perform the
23 claimed genotyping test. The label did not require all
24 physicians to perform the genotyping test, so it was again
25 sufficient that defendants' labels would inevitably lead some

physicians to infringe.

Here defendants' proposed labels do not contain an explicit instruction that defendants' products should be administered for at least 12 weeks. As in *Grunenthal*, defendants' proposed labels likewise do not implicitly require a 12-week treatment.

Plaintiffs have thus failed to meet their burden to show induced infringement, and defendants respectfully request judgment in their favor.

THE COURT: Thank you.

MS. FUNDAKOWSI: Thank you, Your Honor.

THE COURT: Mr. Sipes, will you be responding?

MR. SIPES: If the Court would like, I can respond, Your Honor.

THE COURT: Well, I would like some response.

MR. SIPES: That was my question. I wasn't asking to choose. I wanted to make sure the Court did not just want to just take it under submission.

THE COURT: I'm going to give you a ruling, so I want a response.

MR. SIPES: Okay.

I understand them to be moving principally on the 12-week limitation, so I will respond on that.

The issue here is one of whether or not the labeling induces administration of the drug for at least

1 12 weeks. First, let me go through the evidence that shows
2 that it does, and then I will address the legal standard
3 question.

4 Dr. Steve Ketchum testified about FDA's review
5 and negotiation over the labeling, and pointed to a number of
6 documents both public that would help explain to physicians
7 what the scope of the approval was, and otherwise that showed
8 that the indication for which the drug was approved, treatment
9 of severe hypertriglyceridemia, is chronic, and that treatment
10 is to reduce and maintain triglyceride levels below 500 which
11 requires treatment more than 12 weeks.

12 And, in fact, then Dr. Budoff went on and
13 explained how physicians understand the labeling, and that the
14 labeling is understood to require clinicians to maintain
15 triglyceride levels in these patients under 500, and that as a
16 chronic condition that requires indefinite treatment. He went
17 through all the other elements of the claims as well and
18 showed that they were met too.

19 There's no question that the labeling is
20 instructing physicians that the drug may be used to treat the
21 chronic condition of severe hypertriglyceridemia, to maintain
22 triglycerides below 500, and that that will go on for 12 or
23 more weeks.

24 In fact, Dr. Budoff went on and said that the
25 dosage and administration section instructs doctors rule out

1 the reversible causes. So it in fact specifically directs
2 physicians towards chronic patients, towards 12 or more weeks
3 treatment.

4 In terms of the case law, for example, in
5 *Astrazeneca v. Apotex*, 633 F.3d 1042, Federal Circuit 2010,
6 the Federal Circuit addressed a case in which the (inaudible)
7 had actually carved out an indication for once daily
8 administration that the claim was directed to, their labeling
9 instructed for twice daily administration, but also included
10 titration language, that physicians should seek to use the
11 lowest possible dose, and Federal Circuit found there that
12 that would inevitably lead some physicians to treat once a
13 day, that that was sufficient for induced infringement.

14 That case was actually endorsed by the *Vanda v.*
15 *West-Ward* case, 887 F.3d 1117, Federal Circuit 2018, which
16 rejected the line of argument, I believe, that the defendants
17 are making now, that we need to show that all physicians would
18 be led.

19 In this case, we have clear instructions in the
20 labeling to rule out reversible causes. We have clear
21 instructions to treat patients for a chronic condition. We
22 have descriptions of the clinical study section, which shows
23 as well that the drug is safe and effective for 12 or more
24 weeks. There was no instructions to treat any shorter period
25 of time.

03:56:29 1 And, we have accompanying FDA review documents
03:56:32 2 available to the public that would further inform physicians
03:56:36 3 as to the meaning of the labeling the defendants are
03:56:38 4 proposing, and we think that more than meets the standard for
03:56:42 5 induced infringement in this case.

03:56:44 6 Thank you, Your Honor.

03:56:45 7 THE COURT: Thank you.

03:56:46 8 MR. SIPES: If there are no questions.

03:56:48 9 THE COURT: Any rebuttal?

03:56:50 10 MS. FUNDAKOWSI: If I may, Your Honor.

03:57:06 11 Your Honor, I would like to make two points.
03:57:12 12 Claire Fundakowski again.

03:57:13 13 We believe *Grunenthal*, 919 F.3d 1333 at 1340, is
03:57:20 14 completely on point here. Mr. Sipes mentioned a case, I
03:57:25 15 believe it was the *Astrazeneca v. Apotex* case, in which the
03:57:31 16 dosage and administration section included express
03:57:35 17 instructions for patients to titrate down the medication.

03:57:39 18 *Grunenthal* distinguished that case explaining --
03:57:43 19 and, again, this is at 1340 -- that *Astrazeneca* is in apposite
03:57:51 20 to our facts. There was specific intent that could be
03:57:55 21 inferred, I quote, because the defendant proceeded with a plan
03:57:58 22 to distribute the generic drug knowing that its label imposed
03:58:03 23 infringement problems.

03:58:04 24 In addition, the instructions in the Dosage and
03:58:08 25 Administration Section of the label would inevitably lead some

03:58:12 1 consumers to practice the claimed method of once daily dosing
03:58:16 2 by encouraging users to taper downward to the lower -- lowest
03:58:18 3 effective dose.

03:58:20 4 The language in that Court's decision that "some
03:58:25 5 users" would be led to infringe is because not all physicians
03:58:29 6 would be required to use the lowest effective dose. Not all
03:58:34 7 physicians would be required to taper down to that dose. But
03:58:37 8 there was an express instruction in that case, and that --
03:58:42 9 such an instruction is absent here.

03:58:44 10 I would also like to point out Mr. Sipes
03:58:49 11 referenced the FDA forms that mention chronic use. But as
03:58:56 12 noted -- just a moment, please -- as noted in *Horizon*, 940
03:59:08 13 F.3d 680 at 702, knowing of the possibility of infringement
03:59:16 14 will not suffice.

03:59:18 15 Of course, Vascepa can be used long-term. It
03:59:22 16 can also be used short-term. The label is indifferent to the
03:59:28 17 length of treatment and leaves it entirely up to physician
03:59:32 18 discretion. This does not show active intent to induce
03:59:37 19 infringement and therefore defendants believe judgment should
03:59:41 20 be granted in their favor.

03:59:43 21 That's all, Your Honor.

03:59:44 22 THE COURT: Thank you.

03:59:46 23 I want to take some time to formulate my ruling.
03:59:51 24 I want to continue with the defendants' rebuttal portion.

03:59:58 25 Are you ready to proceed?

04:00:00 1 MR. REIG-PLESSIS: Yes, Your Honor.

04:00:08 2 Your Honor, my name is Eimeric Reig, I'm counsel
04:00:10 3 for the defendants here, and as defendants' first witness, we
04:00:15 4 call Dr. Jonathan Sheinberg.

04:00:20 5 THE COURT: Thank you.

04:00:22 6 THE CLERK: Would counsel like to please have
04:00:24 7 someone come up and retrieve these exhibit binders?

04:00:28 8 MR. REIG-PLESSIS: And we would also ask
04:00:30 9 permission to approach. We have some witness binders, as
04:00:33 10 well, for Dr. Sheinberg.

04:00:35 11 THE COURT: Yes.

04:00:35 12 JONATHAN I. SHEINBERG, M.D.,
04:00:35 13 called as a witness on behalf of the Defendants,
04:00:36 14 was sworn and testified as follows:

04:00:36 14 THE CLERK: Please be seated.

04:01:01 15 Please state for the record your full name and
04:01:07 16 spell your last name.

04:01:08 17 THE WITNESS: Jonathan Sheinberg,
04:01:11 18 S-h-e-i-n-b-e-r-g. Jonathan, J-o-n-a-t-h-a-n.

04:01:38 19 MR. REIG-PLESSIS: Good afternoon,
04:01:39 20 Dr. Sheinberg.

04:01:40 21 THE WITNESS: Good afternoon.

04:01:38 22 DIRECT EXAMINATION

04:01:38 23 BY MR. REIG-PLESSIS:

04:01:41 24 Q Where are you currently employed?

04:01:43 25 A I'm currently employed in Austin, Texas, for Baylor Scott

04:01:47 1 & White Cardiology.

04:01:48 2 Q And what is your current position at Baylor Scott & White
04:01:53 3 Cardiology?

04:01:54 4 A I am a senior staff cardiologist. I am an invasive
04:01:57 5 cardiologist with an interest in preventive cardiology as
04:02:01 6 well.

04:02:01 7 Q Did the defendants retain you to testify as an expert in
04:02:04 8 this case?

04:02:04 9 A Yes, they have.

04:02:05 10 Q Now, apart from this case, do you have any affiliation
04:02:09 11 with the defendants?

04:02:09 12 A I do not.

04:02:10 13 Q And you mentioned that you are a general cardiologist
04:02:16 14 with an interest in preventive cardiology. Could you just
04:02:19 15 explain what preventive cardiology is.

04:02:21 16 A Yes, sir. So I have general cardiology experience, in
04:02:25 17 other words, I practice the full gamut of cardiology from
04:02:29 18 initial evaluation of a patient with intent to prevent that
04:02:32 19 patient from developing coronary disease, taking a patient who
04:02:39 20 already has developed coronary disease and preventing that
04:02:41 21 patient from having a secondary event.

04:02:43 22 I also treat general cardiology patients.

04:02:44 23 I'm also proficient in the catheterization
04:02:47 24 laboratory in which we perform invasive procedures to evaluate
04:02:50 25 problems.

04:02:57 1 THE COURT: Also, would you make sure you speak
04:02:59 2 into the microphone. I want to make sure everyone is able to
04:03:00 3 hear you. Thank you.

04:03:00 4 THE WITNESS: Yes, ma'am.

04:03:01 5 BY MR. REIG-PLESSIS:

04:03:02 6 Q So turning first to DDX 4.1, there is a snapshot on the
04:03:06 7 screen of DX 2225, page 1, which is in your binder as well.

04:03:12 8 Could you identify this document, please.

04:03:14 9 A Yes, this is my CV.

04:03:16 10 Q Does your CV accurately summarize your educational
04:03:19 11 background, work experience, and research?

04:03:21 12 A Yes, it does.

04:03:23 13 MR. REIG-PLESSIS: And, Your Honor, we would
04:03:24 14 move into evidence DX 2225.

04:03:28 15 MS. KEANE: No objection, Your Honor.

04:03:30 16 THE COURT: 2225 is admitted.

04:03:30 17 (Defendants' Exhibit 2225 received in
04:03:32 evidence.)

04:03:32 18 BY MR. REIG-PLESSIS:

04:03:33 19 Q So turning to DDX 4.2, there's another snapshot on the
04:03:39 20 screen of the same exhibit DX 2225.

04:03:42 21 Could you summarize your educational background for
04:03:44 22 the Court, please.

04:03:45 23 A Yes, I can. I graduated with a bachelor's degree from
04:03:48 24 Washington and Lee University. I attended Georgetown
04:03:48 25 University School of Medicine where I received my medical

degree.

At that time I entered active duty with the United States Air Force and did my internship at Georgetown and Fairfax Hospital and my residency at Keesler Air Force Base in internal medicine, that's in Biloxi, Mississippi.

After completion of my internal medicine residency, I went to Wilford Hall Air Force Base -- I'm sorry -- Wilford Hall Medical Center at Lackland Air Force Base, Texas, to finish my fellowship in cardiovascular disease.

After completing that, I continued to serve in the Air Force for an additional four years with a combat deployment overseas before settling in Austin, Texas, in 2004, which is where I am living now.

Q Do you have any board certifications currently?

A I'm Board Certified in cardiovascular disease.

Q And how long have you been a cardiologist?

A This is my 20th year.

Q How many patients do you see per month, approximately, in your cardiology practice?

A I see roughly a 100 patients or more per month -- I'm sorry, per week, which averages about 400 or so, plus or minus, per month.

Q Do you treat patients with elevated triglycerides?

A Every day.

Q Do you treat patients with triglyceride levels above 500?

04:05:10 1 A Yes, I do.

04:05:11 2 Q How often?

04:05:12 3 A Relatively frequently, on the order of approximately 20
04:05:18 4 to 30 per month.

04:05:19 5 Q Have you prescribed Vascepa before?

04:05:21 6 A Yes, I have.

04:05:22 7 Q And have you taught courses relating to cardiology?

04:05:27 8 A Yes, I have. I have been an instructor and a professor
04:05:31 9 of medicine both at the University Uniform Health Science
04:05:36 10 Center in Bethesda, Maryland, as well as Wright State
04:05:42 11 University in Dayton, Ohio.

04:05:42 12 COURT REPORTER: Slow down, please.

04:05:43 13 THE WITNESS: Sorry. So the Uniform Services
04:05:45 14 University in Bethesda, Maryland, as a Clinical Professor, as
04:05:50 15 well as an Assistant Professor at Wright State University in
04:05:53 16 Dayton, Ohio. I'm currently an Assistant Professor of
04:05:58 17 Medicine at the University of Texas Medical Branch in
04:06:02 18 Galveston.

04:06:03 19 BY MR. REIG-PLESSIS:

04:06:03 20 Q And do you conduct any other activities related to
04:06:06 21 cardiology?

04:06:07 22 A Yes, I do. As the first page of my CV pointed out, not
04:06:12 23 only am I a cardiologist, but I'm also one of the few
04:06:16 24 physicians in the United States who is a sworn police officer.

04:06:19 25 I serve in that capacity, not only as an officer,

04:06:23 1 but I work within the Department of Justice to develop and
04:06:28 2 create wellness programs which we institute throughout the
04:06:31 3 United States and Canada to keep police officers and other
04:06:35 4 first responders healthy as well.

04:06:38 5 Q Now, do you have any publications on your CV?

04:06:41 6 A I do not.

04:06:42 7 Q And why not?

04:06:43 8 A I am a practicing, busy, what we like to refer to as,
04:06:48 9 quote, in the trenches, cardiologist. With a very busy
04:06:52 10 clinical practice, there's really no time left to devote to
04:06:57 11 research.

04:06:57 12 In fact, we often in -- those of us who practice in
04:07:02 13 busy, clinical practices often say that we are penalized if we
04:07:07 14 spend time doing research because at that time we are not
04:07:10 15 actively seeing patients and we are not generating volume
04:07:15 16 through the clinic.

04:07:16 17 So I do not have any research publications in that
04:07:19 18 regard.

04:07:20 19 Q Now, we've heard some testimony already today about
04:07:23 20 approved drug labels. Are those labels generally directed to
04:07:27 21 researchers or to clinicians?

04:07:29 22 A They're directed towards clinicians.

04:07:32 23 Q And are you a clinician?

04:07:34 24 A Yes, sir, I am.

04:07:36 25 MR. REIG-PLESSIS: Defendants now tender

04:07:37 1 Dr. Sheinberg as an expert in the field of cardiology.

04:07:41 2 MS. KEANE: No objection, Your Honor.

04:07:41 3 MR. REIG-PLESSIS:

04:07:43 4 Q Dr. Sheinberg, do you have slides --

04:07:44 5 THE COURT: Is this just a general field of
04:07:47 6 cardiology?

04:07:47 7 MR. REIG-PLESSIS: Yes, Your Honor.

04:07:48 8 THE COURT: Is that the motion?

04:07:49 9 You have to wait for me to rule. So, is that
04:07:52 10 the motion?

04:07:52 11 MR. REIG-PLESSIS: Yes, Your Honor, in the
04:07:53 12 general field of cardiology.

04:07:55 13 THE COURT: There's no objection, so the request
04:07:57 14 is granted.

04:07:57 15 BY MR. REIG-PLESSIS:

04:07:58 16 Q Dr. Sheinberg, do you have slides to assist the Court
04:08:01 17 with your testimony today?

04:08:02 18 A Yes, I do.

04:08:03 19 Q And are the documents cited in those slides documents you
04:08:06 20 relied on in forming your opinions?

04:08:08 21 A Yes, they are.

04:08:09 22 Q So turning now to DDX 4.3, could you summarize the
04:08:17 23 opinions you'll be presenting in your testimony today.

04:08:19 24 A Yes, I will.

04:08:20 25 I will -- it will be my opinion this afternoon that

04:08:26 1 severe hypertriglyceridemia is not necessarily a chronic
04:08:29 2 condition which requires indefinite drug treatment, and I also
04:08:33 3 will opine that severe hypertriglyceridemia can be treated
04:08:37 4 with a short course of drug therapy followed by diet and
04:08:41 5 exercise to maintain the triglyceride reductions that we
04:08:44 6 have seen.

04:08:45 7 Q And, Doctor, are you offering those opinions today in the
04:08:49 8 context of the indicated use for Vascepa and defendants'
04:08:52 9 products to treat, quote, severe hypertriglyceridemia?

04:08:56 10 A Yes, I am.

04:08:58 11 Q So turning to DDX 4.4, do you also have specific opinions
04:09:03 12 on defendants' product labels?

04:09:05 13 A Yes, I do. It is the opinion that I will share today
04:09:09 14 that defendants' labels do not encourage, recommend, promote,
04:09:13 15 or require administration -- administering their product for
04:09:16 16 any duration, let alone at least 12 weeks, to achieve specific
04:09:20 17 effect on the lipids, including a minimum percent reduction in
04:09:25 18 triglycerides, to avoid an increase in LDL, and to cause a
04:09:31 19 reduction of apolipoprotein B levels.

04:09:33 20 I will also show this can be done without concurrent
04:09:37 21 lipid-altering therapy.

04:09:39 22 Q Turning to DDX 4.5, in forming your opinions did you
04:09:43 23 analyze the claims that are asserted by Amarin in this case
04:09:46 24 against the defendants?

04:09:47 25 A Yes, I have. '929 patent claims 1 and 5; '728 patent

claims 1 and 16; '715 patent claim 14; '677 patent claims 1 and 8; '652 patent claim 1; and '560 patent claims 4 and 17.

Q And are you familiar with those claims which are in the patents that are in your binder?

A Yes, I am.

Q Turning to DDX 4.6, which limitations of the asserted claims did you specifically analyze?

A In regarding the at least 12 weeks duration of drug treatment limitation, that is in all 10 asserted claims.

In regards to the specific effects on lipid levels limitation, which includes the minimum triglyceride reductions;

The no increase in LDL; and

The reduction in apolipoprotein B that is seen in nine claims which are all asserted claims except '929 patent claim 1; and

The limitation of no concurrent lipid-altering therapy, which we will discuss, which includes statins, but not limited to that drug class is in three claims;

'728 patent claims 1 and 16; as well as '715 patent claim 14.

Q And are you addressing any other limitations of the claims in your testimony besides the limitations described in DDX 4.6?

A No, sir, I am not.

04:11:21 1 Q So turning to DDX 4.7, there is a snapshot from DX 1500,
04:11:27 2 which I understand is on the admitted exhibits list, could you
04:11:30 3 point out the three categories of limitations that you
04:11:34 4 analyzed in an exemplary asserted claim.

04:11:37 5 A Yes. In this example, which is '728 patent claim, you
04:11:41 6 can see that it does have all three of the limitations.
04:11:45 7 Starting with the yellow highlighted section number 1 for a
04:11:49 8 12-week duration, as you can see it describes that acid or
04:11:55 9 esters for a period of 12 weeks.

04:11:57 10 In regards to the specific lipid effects, the
04:11:59 11 example here which is seen in nine claims, to effect a
04:12:02 12 reduction in triglycerides without substantially increasing
04:12:06 13 LDL.

04:12:07 14 And the third example, which is highlighted in
04:12:09 15 orange, is seen under the section after 1500 milligrams per
04:12:15 16 deciliter, talking about individuals who do not receive
04:12:18 17 concurrent lipid-altering therapy as this is one of the claims
04:12:22 18 that has all three components associated with it.

04:12:25 19 Q So turning now to DDX 4.8, there are snapshots on the
04:12:30 20 screen of the Court's claim construction order, and the
04:12:32 21 parties' stipulation on agreed upon constructions which are
04:12:36 22 ECF numbers 135 and 83. Did you apply the constructions in
04:12:41 23 these documents in forming your opinions in this case?

04:12:43 24 A Yes, I have.

04:12:47 25 Q So turning to DDX 4.9, what are the topics you intend to

04:12:52 1 address in your testimony?

04:12:53 2 A There will be two specific topics. The first I will give
04:12:56 3 background regarding the concept of severe
04:12:59 4 hypertriglyceridemia, and we will -- I will also talk about
04:13:03 5 how Vascepa is used, and then we will discuss the
04:13:06 6 noninfringing analysis that I performed.

04:13:11 7 Q So turning to DDX 4.10, there is a snapshot on the screen
04:13:16 8 of DX 1876, page 99. We understand this exhibit has also been
04:13:23 9 admitted. Could you identify this document.

04:13:25 10 A Yes, I can. This is the National Cholesterol Education
04:13:30 11 Program, the NCEP expert panel on detection, evaluation, and
04:13:35 12 treatment of high blood cholesterol levels in adults,
04:13:39 13 otherwise known as the Adult Treatment Panel, or ATP III final
04:13:45 14 report. It was published in circulation in 2002.

04:13:47 15 And, as this document goes on to describe in the
04:13:49 16 highlighted area below, it states that if triglycerides are
04:13:53 17 very high, which is greater than or equal to 500 milligrams
04:13:58 18 per deciliter, attention turns first to the prevention of
04:14:01 19 acute pancreatitis.

04:14:03 20 Q And what is severe hypertriglyceridemia or very high
04:14:07 21 triglycerides?

04:14:09 22 A In terms of the definition here, greater than
04:14:13 23 500 milligrams per deciliter, is that the --

04:14:15 24 Q Yes. Just in general what is it?

04:14:17 25 A It's a situation in which hyper means too many.

04:14:23 1 Triglyceridemia means triglycerides in the blood, and so it's
04:14:27 2 too many triglycerides in the blood.

04:14:29 3 Q Now, is severe hypertriglyceridemia a discrete disease?

04:14:35 4 A It is not actually a discrete disease. It is more of a
04:14:39 5 downstream consequence of multiple potential etiologies or
04:14:44 6 causes.

04:14:45 7 Q Why does severe hypertriglyceridemia require treatment?

04:14:49 8 A Because if it is not treated, we know it can cause two
04:14:52 9 different issues, the first which is described here as
04:14:55 10 pancreatitis. Pancreatitis, which has already been described
04:14:59 11 as a very painful, horrible condition in which the pancreas
04:15:04 12 becomes inflamed and essentially begins to digest itself.

04:15:09 13 Not only is it painful, but it carries with it a
04:15:12 14 rather high mortality rate. In other words, it can cause
04:15:15 15 death in a relatively frequent amount of people who suffer
04:15:15 16 from it.

04:15:19 17 And we also know that there is an association with
04:15:20 18 elevated triglycerides in cardiovascular risk.

04:15:23 19 Q Now, if a patient is at risk for pancreatitis, do you
04:15:27 20 delay treating that patient with triglyceride-lowering drugs?

04:15:30 21 A Absolutely not. If I have a patient that is at risk for
04:15:34 22 this potential life-threatening complication, we treat that
04:15:38 23 person aggressively from day one.

04:15:40 24 Q Do you necessarily treat patients differently depending
04:15:45 25 on whether their triglycerides are above or below 500?

04:15:49 1 A There is no magic thing that happens at 500. If I have
04:15:54 2 someone who has triglycerides of 400, someone who has
04:15:59 3 triglycerides of 550 or 600, I will look at that person
04:16:02 4 relatively equivalently and treat those people aggressively to
04:16:07 5 prevent the sequelae or the consequences that those
04:16:11 6 triglycerides would potentially result in.

04:16:14 7 Q So turning to DDX 4.11, there is a snapshot on the screen
04:16:19 8 of DX 1982, page 2 which is already in evidence. Could you
04:16:23 9 identify this document.

04:16:25 10 A Yes, I can.

04:16:26 11 This is the website for Vascepa, and the website
04:16:32 12 goes on to describe what are the causes for
04:16:36 13 hypertriglyceridemia, and it lists five specific issues. The
04:16:40 14 first two are highlighted in yellow here.

04:16:43 15 Oftentimes, as the testimony has shown throughout
04:16:47 16 the day, these two things run hand-in-hand, but according to
04:16:50 17 the website here it quotes, "Here are some ways that
04:16:54 18 triglyceride levels may become very high."

04:16:56 19 The first is diet and lack of exercise. This
04:17:01 20 combination of poor diet and a sedentary lifestyle is the
04:17:06 21 cause of most of what we see. I would imagine that's why they
04:17:10 22 are the two items that are listed first. And after practicing
04:17:13 23 for 20 years with 25,000 patients in my population that I see,
04:17:17 24 it is no question in my mind that these are the primary causes
04:17:21 25 of hypertriglyceridemia.

Under the diet section, it says what you eat and drink, especially alcohol and processed carbohydrates. Quite frankly, the concept, at least where I practice in Texas, sugared sodas should be listed on that list because it is a considerable problem that we see. We also know that our patients are likely not getting the exercise that they need.

Besides diet and exercise, we see certain medical conditions which can cause hypertriglyceridemia such as diabetes.

And I would go on to also say, in regards to diabetes, most of the diabetes that we treat in cardiology is Type II diabetes, it's diabetes that results from what we call insulin resistance which is a diabetes not from a genetic, discrete problem in which the pancreas doesn't produce enough insulin, it's from a metabolic problem which is basically a diet and exercise issue.

The fourth thing on the list are specific drugs, which includes hormones and certain blood pressure medications.

And the last thing on this list, it says genetics, and that's a rather broad term, which if I may define it a little bit at this moment.

There are two -- we can think of the genetic issue as basically two different discrete issues. There is a definitive, genetic abnormality in a very small minority of

our patients that are missing the genetic ability, or missing the ability to code for certain enzymes or proteins, which, for example, cause triglycerides to be broken out of certain cholesterol particles.

For example, there's an enzyme called lipoprotein lipase, and if there is an individual who does not have that enzyme, that individual will have severely elevated triglycerides which are what we call refractory or very difficult to treat.

There are other genetic abnormalities. They've already been mentioned here this morning and this afternoon. But, 98 or more of our patients -- 98 percent or more of our patients do not have those discrete genetic abnormalities.

What they may have is what we like to call a genetic predisposition. In medicine we understand that there are genetic predispositions for everything, for how tall people are, for how people respond to certain diets and exercise.

We all know people who -- the layman's term is they look at a pizza and they gain weight. We know people who are able to eat very little and still not achieve optimal body mass, and the other side of the spectrum is true as well. We know people who can eat everything on their plate and they never gain weight.

We have genetic proclivities that influence how we respond to everything in our lives, and there are people who

1 have a genetic proclivity to have elevated triglycerides
2 without having the specific genetic abnormality which relates
3 in exceedingly elevated triglyceride levels.

4 Q So can a patient be genetically predisposed to
5 hypertriglyceridemia that is not severe?

6 A Absolutely.

7 Q Now, apart from those listed on Amarin's website, are
8 there other cases of severe hypertriglyceridemia?

9 A There are. Under medical conditions we have -- we see
10 renal failure. We see people who smoke have an increased
11 risk. We know in pregnancy, especially in the last trimester,
12 women can have hypertriglyceridemia which sometimes becomes
13 severe.

14 So there are certainly other things that this list
15 is exclusive of.

16 Q Are there short-term causes of severe
17 hypertriglyceridemia?

18 A Absolutely. We know it for a fact that when people
19 overindulge in certain diets, a diet which is very high in
20 simple sugars or alcohol, and potentially reduce their
21 activity -- the best example of this I can think of is you
22 take someone who goes on a cruise, who is potentially
23 genetically predisposed to have elevated triglycerides.
24 They're on the cruise for the week. They are eating at the
25 buffet, having as many desserts as they want, they're not

04:21:42 1 exercising. They're consuming considerable amounts of
04:21:46 2 alcohol.

04:21:46 3 That individual, who is genetically predisposed for
04:21:50 4 an elevation of triglycerides, even severe elevation of
04:21:53 5 triglycerides, after that cruise there's a very good chance
04:21:57 6 that individual will be over 500.

04:21:59 7 So there are acute conditions. You remove those
04:22:01 8 acute insults, you take the person off the cruise, they go
04:22:05 9 back on their lifestyle, and that situation of
04:22:10 10 hypertriglyceridemia can potentially resolve. So there are
04:22:13 11 certainly other acute reasons.

04:22:15 12 Q Now, does Amarin's website indicate anywhere that the use
04:22:19 13 of Vascepa is limited to patients with genetic abnormalities
04:22:24 14 causing severe hypertriglyceridemia?

04:22:26 15 A No, sir, it does not.

04:22:27 16 Q And what are the typical triglyceride levels of patients
04:22:30 17 with those types of genetic abnormalities?

04:22:34 18 A The genetic abnormalities that I mentioned, the ones that
04:22:38 19 have already been mentioned earlier in testimony, are
04:22:39 20 typically well over 1000 to 2000.

04:22:43 21 Again, there's a considerable variability, but those
04:22:47 22 people who have discrete genetic conditions typically have
04:22:52 23 triglycerides which are multiples of 500.

04:22:54 24 Q So generally, in the triglyceride range of 500 to 1000,
04:22:58 25 does that include patients with genetic abnormalities usually?

04:23:03 1 A It can, but usually it does not. As we get higher, up to
04:23:08 2 that 1000 level range, the genetic abnormality will become
04:23:13 3 more prevalent.

04:23:15 4 But when we talk between 500, as we get higher in
04:23:17 5 that range, there are still plenty of people who will have
04:23:21 6 severe hypertriglyceridemia which is not from a discrete
04:23:24 7 genetic abnormality.

04:23:26 8 Q And when you say "plenty of people," can you estimate
04:23:29 9 what percent of patients would have it?

04:23:32 10 A Ninety-seven plus percent, 98 percent.

04:23:35 11 Q And just to be clear, that's 98 percent without a genetic
04:23:35 12 abnormality?

04:23:37 13 A The discrete -- excuse me. The discrete genetic
04:23:39 14 abnormalities really occur in potentially 2 percent of the
04:23:44 15 population that we see.

04:23:47 16 Q So turning now to DDX 4.12, there's a snapshot on the
04:23:54 17 screen of DX 1953, page 29. Could you identify this document.

04:23:58 18 A Yes, I can. This is Amarin's validity contentions.

04:24:02 19 This document goes on to say that -- in the first
04:24:06 20 paragraph here,

04:24:09 21 "Persons of ordinary skill in the art also
04:24:13 22 understood that both diet and exercise level could
04:24:17 23 have significant impacts on triglyceride levels.

04:24:20 24 Heavy consumption of carbohydrates, certain kinds of
04:24:25 25 fats and/or alcohol was understood to lead to

increased triglyceride levels."

The document further goes on to say in the second paragraph,

"In contrast, it was understood that regular exercise could offset the triglyceride effects of some dietary factors and decreased triglyceride levels. Accordingly, the lack of exercise and/or sedentary lifestyle are known to correlate with higher triglyceride levels."

Q Do you agree with these statements in Amarin's validity contentions in this case?

A Absolutely. This is what I would consider the absolute, primary reason many of our patients suffer from hypertriglyceridemia.

MR. REIG-PLESSIS: And, Your Honor, we would move the admission of DX 1953.

MS. KEANE: Your Honor, plaintiffs object to the admission --

THE COURT: Would you make sure you speak into the microphone.

MS. KEANE: Yes, Your Honor.

Plaintiff's object to the admission of DX 1953. These are Amarin's preliminary validity contentions. It is a document containing attorney argument. It is not evidence of fact, and it, therefore, is not appropriate admissible

04:25:35 1 evidence.

04:25:35 2 We are aware of there is case law --

04:25:39 3 THE COURT: Isn't it already part of the record?

04:25:42 4 MS. KEANE: They have not been admitted, Your

04:25:43 5 Honor.

04:25:43 6 THE COURT: Well, wasn't it a record in terms of
04:25:47 7 it being filed with the Court on the docket?

04:25:49 8 MS. KEANE: No, Your Honor. It was not filed,
04:25:50 9 it was just exchanged amongst the parties. It's a preliminary
04:25:55 10 statement --

04:25:55 11 THE COURT: Oh, I see.

04:25:56 12 MS. KEANE: -- of positions of counsel.

04:25:57 13 THE COURT: I'm sorry to interrupt. But, you
04:25:59 14 were saying --

04:26:00 15 MS. KEANE: Yes. We believe there's a case from
04:26:03 16 the District of Hawaii that's directly on point, that
04:26:07 17 preliminary contentions, one, are not evidence of fact, and,
04:26:09 18 two, they are not party admission either. And the cite for
04:26:14 19 that is 2015 WL 1117993, and the title is *Kowalski v. Anova*
04:26:39 20 *Food*.

04:26:39 21 THE COURT: What's your response?

04:26:39 22 MR. REIG-PLESSIS: Well, Your Honor, a couple
04:26:41 23 responses. I think we're a little puzzled by the objections
04:26:44 24 since these are Amarin's own statements and contentions in
04:26:48 25 this very case. We submit that they would be at least party

admissions under Federal Rule of Evidence 801(d)(2).

We're aware of the *Kowalski* case which plaintiffs have cited to us. It's an unpublished case from the District of Hawaii which was not applying this court's patent rules.

Obviously these contentions were served under this court's patent rules on defendants. It is far too late for plaintiffs to amend the contentions. These statements were never amended.

We tried to avoid having to move these into evidence by simply adding Amarin's own statements of fact verbatim, a stipulated fact into the Pretrial Order. Amarin refused. It seems they are backing away from these statements that, again, were their own contentions of fact.

Now, you know, we're not arguing they're bound by these contentions as judicial admissions, we would just say that they are at least evidentiary admissions that should come in and FRE 801.

I should just add there are also cases going the other way. We cited one such case from the Eastern District of Texas which hears almost -- many, many patent cases, and that found the other way.

THE COURT: Well, regardless of how other district courts have ruled, I overrule the objection. I find that because the validity contentions were exchanged as part

of the Court's Local Rule, the party that offered the contentions are bound by their contentions and now cannot try to seek to exclude them, therefore, the objection is overruled.

Exhibit 1953 is admitted.

(Defendants' Exhibit 953 received in evidence.)

MR. REIG-PLESSIS: Thank you, Your Honor.

BY MR. REIG-PLESSIS:

Q So turning now to DDX 4.13, there's a snapshot on the screen of DX 1957, page 6. Could you identify this document, please.

A Yes, I can. This is an excerpt from the Karalis paper, *A Review of Clinical Practice Guidelines For the Management of Hypertriglyceridemia*. It was published in *Advanced Therapeutics* in 2017 out of the University of Pennsylvania.

Dr. Karalis goes on to describe in this paper, "The cornerstone for the treatment of hypertriglyceridemia is lifestyle intervention with diet and exercise."

He goes on further to describe,

"However, pharmacologic therapy to lower triglycerides may be considered based on an individual's cardiovascular risk and how high the level of triglycerides are."

Q So based on Karalis, is pharmacologic therapy to lower

04:29:18 1 triglycerides in patients with severe -- excuse me -- with
04:29:21 2 hypertriglyceridemia always required?

04:29:22 3 A No, they are not always required.

04:29:24 4 MR. REIG-PLESSIS: And, Your Honor, we would
04:29:26 5 move into evidence DX 1957.

04:29:29 6 MS. KEANE: No objection.

04:29:33 7 THE COURT: I'm sorry. I didn't hear. Did you
04:29:35 8 say no objection?

04:29:35 9 MS. KEANE: No objection.

04:29:36 10 THE COURT: DX 1957 is admitted.

04:29:36 11 (Defendants' Exhibit 1957 received in
04:29:41 evidence.)

04:29:41 12 MR. REIG-PLESSIS: Thank you, Your Honor.

04:29:43 13 BY MR. REIG-PLESSIS:

04:29:43 14 Q So turning to DDX 4.14, Dr. Sheinberg, were you in the
04:29:48 15 courtroom were Mr. Klein presented the testimony on the screen
04:29:51 16 from Dr. Budoff during opening statements?

04:29:51 17 A Yes, I was.

04:29:52 18 Q And were you in the courtroom when Dr. Budoff confirmed
04:29:56 19 this testimony during his examination?

04:29:58 20 A Yes, I was.

04:29:59 21 Q And how does Dr. Budoff's clinical -- excuse me. How
04:30:03 22 does Dr. Budoff's testimony on DDX 4.14 compare with your own
04:30:08 23 clinical experience?

04:30:10 24 A Let me first describe what Dr. Budoff is saying here.

04:30:14 25 His -- the question was,

04:30:16 1 "And so is it consistent with your experience
04:30:19 2 that roughly one-fifth of patients with severe
04:30:24 3 hypertriglyceridemia are able to reduce their
04:30:27 4 triglyceride levels below 500 through diet and
04:30:30 5 exercise alone?"

04:30:31 6 To which Dr. Budoff replies yes.

04:30:34 7 And to answer your question after reading that,
04:30:36 8 it is consistent, however, my experience is even more so.
04:30:39 9 Dr. Budoff will say one-fifth of his patients, my experience
04:30:44 10 is it's more closely with -- closer to 70 percent to
04:30:49 11 75 percent of my patients can reduce their triglycerides below
04:30:54 12 500 through diet and exercise alone.

04:30:59 13 Q And why do you believe your experience differs from
04:31:03 14 Dr. Budoff's?

04:31:04 15 A I can simply tell you that in my practice I see -- there
04:31:09 16 may be several reasons. Number one, we're in different parts
04:31:12 17 of the country so I can only comment on what the dietary
04:31:17 18 makeup for the local central Texas patient population is,
04:31:22 19 which, unfortunately, Texas has a significantly high rate of
04:31:26 20 obesity which is one of the highest in the country.

04:31:30 21 Also, the type of patients that I see, I am in a
04:31:33 22 primary setting. In other words, I have -- most of my
04:31:37 23 patients are referred to me by either word-of-mouth, they come
04:31:42 24 in directly, or they come from a primary care physician. I do
04:31:47 25 not have secondary, tertiary referrals.

04:31:52 1 In other words, I don't work at a large center which
04:31:55 2 specializes or is known to be a research center that would
04:31:58 3 receive more difficult cases.

04:32:00 4 So I think the combination of my initial patient
04:32:03 5 population -- and, again, I cannot speculate on Dr. Budoff's
04:32:07 6 population or how his practice runs, but I do see quite a bit
04:32:12 7 of individual referrals, patients who do not go through other
04:32:17 8 individuals who are treating their lipids before they come to
04:32:21 9 me.

04:32:21 10 Q And is the indicated use of Vascepa to treat severe
04:32:25 11 hypertriglyceridemia limited to patients for secondary or
04:32:30 12 tertiary referrals?

04:32:31 13 A It is not.

04:32:32 14 Q So turning now to DDX 4.15. There's a snapshot on the
04:32:39 15 screen of DX 1960, page 38. Could you identify this document,
04:32:43 16 please.

04:32:43 17 A Yes, I can. This is an excerpt from a textbook on
04:32:48 18 dyslipidemia by Pete Kwiterovich. It is written out of Johns
04:32:54 19 Hopkins, and the chapter 7 which I am quoting here is
04:32:56 20 *Disorders of Hypertriglyceridemia*, written by Dr. Michael
04:33:02 21 Miller.

04:33:02 22 It goes on to say that, "in addition to" -- and this
04:33:05 23 abbreviation of HFCS stands for high fructose corn syrup --

04:33:11 24 "A diet high in carbohydrates may lead to an
04:33:17 25 elevation of triglycerides."

04:33:17 1 It goes on further towards the bottom and it
04:33:20 2 says, "Regardless of macronutrient intake," which
04:33:23 3 means whether it's protein or fat or carbohydrate,
04:33:28 4 "the most potent manner for reducing triglycerides is
04:33:32 5 through weight reduction,"
04:33:33 6 which is absolutely consistent with what I see in my clinical
04:33:37 7 practice daily.

04:33:38 8 Q And do you understand from the testimony earlier today
04:33:40 9 that Michael A. Miller was Amarin's claim construction expert
04:33:45 10 in this case?

04:33:46 11 A Yes, I do.

04:33:47 12 Q So turning now to DDX 4.16, there's a snapshot on the
04:33:53 13 screen of DX 1957, page 10.

04:33:57 14 Now, once a patient starts a triglyceride lowering
04:34:00 15 drug, can it be discontinued?

04:34:02 16 A Yes, it can.

04:34:04 17 Q And could you explain.

04:34:06 18 A Yes, I can. This is an excerpt from that Karalis article
04:34:10 19 that we discussed. The excerpt says,

04:34:12 20 "If the triglyceride levels fall to normal or
04:34:15 21 borderline level with lifestyle changes and a
04:34:18 22 combination of lipid-lowering therapy, consideration
04:34:21 23 may be given to discontinuing the nonstatin
04:34:24 24 triglyceride-lowering medication."

04:34:29 25 And then if you look at the bottom of the slide,

there's a simple graphic which represents the initiation of an individual's visit with a physician in which a short course of drug therapy is initiated, along with a lifestyle modification, which again is a diet, reconstruct -- diet construction and an exercise prescription.

That is continued for a brief amount of time, and then the drug can be discontinued when the triglycerides are less than 500 milligrams per deciliter, and we can maintain that with diet and exercise alone.

Q And is the treatment depicted on DDX 4.16 a medically reasonable way to treat a patient with a triglyceride-lowering drug?

A Absolutely.

Q So turning to DDX 4.17, I'll represent to you that this is a snapshot from Amarin's trial brief in this matter which was filed as ECF number 327, at pages 12 and 13, and could you just let us know whether you agree with the statements in this paragraph?

A So in order to give you that answer, I actually have to dissect this paragraph a little bit. That's a little bit more complicated than just answering yes or no because certain things I do agree with, and other things I would like to make a clarification because I do not agree with.

It goes on to say that,

"Severe hypertriglyceridemia is

04:35:57 1 life-threatening because it puts patients at acute
04:36:01 2 risk of pancreatitis."

04:36:02 3 I think there's no question. We all agree on
04:36:05 4 that.

04:36:05 5 It goes on to say,

04:36:06 6 "It is chronic because it is typically caused
04:36:08 7 by genetic factors."

04:36:10 8 Well, if we take that portion of this document
04:36:13 9 here, I would argue that it is not chronic and that it is not
04:36:18 10 typically caused by genetic factors. I think my testimony so
04:36:23 11 far has really been evident that the chronicity of this is not
04:36:27 12 something that is definitive. We -- and I've given examples
04:36:32 13 of individuals who can have acute elevations of triglycerides.

04:36:35 14 When we talk about genetic factors, again, I
04:36:38 15 like to make sure that we delineate the two different types of
04:36:42 16 genetic factors that we're talking about, the absolute
04:36:45 17 discrete genetic abnormality, which is a very small percentage
04:36:50 18 of our patients, versus a genetic predisposition or
04:36:54 19 predilection to develop a problem.

04:36:57 20 So to say that it is chronic, which is typically
04:37:00 21 caused by genetic factors, I do not believe the way it's
04:37:03 22 written here is correct.

04:37:05 23 It goes on to say that this cannot be cured
04:37:07 24 through medication, and, again, that sentence or that
04:37:10 25 statement here, we will agree that this type of problem can't

04:37:15 1 be -- there's no cure.

04:37:17 2 It's a treatment, not a cure, which is very
04:37:21 3 different than someone who has a pneumonia. In that case, we
04:37:25 4 give medication to cure a pneumonia. Here, we use a
04:37:29 5 treatment.

04:37:29 6 The problem is the treatment is not necessarily
04:37:32 7 through medication. The treatment, and like I've testified,
04:37:34 8 is really lifestyle limiting.

04:37:37 9 So, for example -- it's a silly example, but if
04:37:41 10 you have a rowboat that has a hole in it that is filling with
04:37:44 11 water and you keep scooping out the water, you aren't going to
04:37:48 12 get anywhere. You have to fix the underlying problem. You
04:37:51 13 have to patch that hole.

04:37:53 14 In that example, patching the hole is fixing the
04:37:57 15 underlying lifestyle problem. Unless you fix that problem,
04:38:01 16 you can bail water all day long, and you're never going to
04:38:05 17 have this problem fixed.

04:38:06 18 The document goes on further to say,
04:38:10 19 "If triglyceride-lowering medications are
04:38:12 20 ceased, the severely hypertriglyceridemic patient
04:38:16 21 will have triglyceride levels which will typically
04:38:19 22 rise again to dangerous premedication levels."

04:38:22 23 And, again, to go back to the example that I
04:38:24 24 said earlier, it's not if the medications are ceased but if
04:38:29 25 the lifestyle modifications are not sustained and prolonged.

04:38:33 1 This is also manifested in individual patients who yo-yo on
04:38:37 2 their weight.

04:38:38 3 We take someone who has what we call metabolic
04:38:42 4 syndrome, they're overweight, they're sedentary, they're
04:38:48 5 diabetic or pre-diabetic, we get those individuals well
04:38:50 6 treated, we get them on a diet and exercise program, they lose
04:38:54 7 weight, they are no longer diabetic or pre-diabetic, their
04:38:54 8 blood pressure issues resolve.

04:38:58 9 If they maintain that, they're great. If they
04:39:00 10 don't, they gain their weight back, they go right back to the
04:39:05 11 same risks they had.

04:39:06 12 In this case, if they don't maintain the dietary
04:39:09 13 and lifestyle changes that were prescribed, their
04:39:12 14 triglycerides will, again, typically rise to the dangerous
04:39:16 15 levels. But I would argue that it's not the medication that's
04:39:19 16 doing it, it's the lifestyle.

04:39:21 17 This document further goes on to say,
04:39:24 18 "To prevent triglyceride levels from
04:39:27 19 returning to dangerous pretreatment levels, standard
04:39:32 20 medical practice is to administer triglyceride-
04:39:34 21 lowering medications to severely hypertriglyceridemic
04:39:37 22 patients chronically, not on a short-term,
04:39:40 23 intermittent basis."

04:39:42 24 And, again, throughout this example I've laid
04:39:45 25 out several scenarios in which the triglyceride medicine does

not need to be given chronically. It can be given on a short-term basis, and it can be given on an intermittent basis.

To go back to the example that I just mentioned, if I have an individual who was able to effect a good diet and exercise shift, they turn the leaf over, they're exercising, they're not smoking, they're not consuming carbohydrate-rich and sugar-rich foods, that person will have a reduction in their triglycerides.

If that person goes back to their previous lifestyle, their triglycerides will rise. They may now have a need, again, for hypertriglyceride-lowering medicines. They may also have a need again for anti-hypertensive medicines or diabetic medicine.

So all these medicines can be used on a short-term, intermittent basis.

Q Now, do you also have slides on how Vascepa is prescribed in clinical practice?

A Yes, sir, I do.

Q How often do you personally prescribe Vascepa?

A I prescribed Vascepa probably 15 to 20 times per month.

Q Are there similar products that you use more often than Vascepa?

A Yes, there are. I use the -- I use generic version of Lovaza, and I often use over-the-counter fish oil products as

04:41:10 1 well. There are some over-the-counter products that contain
04:41:13 2 DHA, DPA, and EPA, and some that just contain EPA. So, I use
04:41:20 3 a very similar products on a daily basis in my practice.

04:41:25 4 Q So turning now to DDX 4.19, there's a snapshot on the
04:41:29 5 screen of DX 2248, page 2, and this exhibit is already in
04:41:32 6 evidence.

04:41:33 7 When you do use Vascepa, Dr. Sheinberg, what are
04:41:37 8 your main reasons for prescribing it?

04:41:40 9 A So I will start -- there are several reasons, and let me
04:41:43 10 start with the indications that are listed here from the
04:41:46 11 package insert.

04:41:48 12 The first indication, which throughout the last two
04:41:50 13 days of testimony we've come to know as the REDUCE-IT
04:41:54 14 indication, which is the indication to reduce the risk of
04:41:57 15 heart attack, stroke, revascularization, which is bypass and
04:42:02 16 stint, and unstable angina, really chest pain requiring
04:42:05 17 hospitalization in the set population which are individuals
04:42:09 18 who have cardiovascular disease or individuals who have
04:42:13 19 diabetes and two more risk factors.

04:42:15 20 The second indication is an adjunct diet, which is
04:42:20 21 what we've described here as the previous indication, which is
04:42:23 22 to reduce -- or the MARINE indication, which is to reduce
04:42:27 23 triglyceride levels in adults with triglycerides over 500.

04:42:31 24 But I will also point out there are other reasons
04:42:34 25 which Vascepa is used in my practice, one of which is those of

us who use what we call advanced lipid testing, which is lipid testing or cholesterol testing which doesn't just focus on the amount of cholesterol, we actually focus on the quality of cholesterol.

So, for example, LDL, which is bad cholesterol, occurs in many different sizes. We know these products have an improvement in cholesterol quality.

We also know these products, which is icosapent ethyl, has an improvement in inflammation, and we now understand that when someone has a heart attack, it is actually resulting from an inflammatory change within that artery.

So our understanding of the pathogenesis of heart disease is based on our understanding of the inflammatory changes within the artery. Icosapent ethyl effectively reduces those inflammatory changes which may or may not lead to the benefits that we see here, that's been speculated over and over again.

So the reality is there are multiple reasons to use this medication.

Q Now, just focusing on the two on-label uses of Vascepa, does the REDUCE-IT indication, as the parties have been referring to it, have anything to do with the original MARINE indication?

A They are completely separate indications which affect

1 completely different patient populations.

2 I can tell you in my practice of over 400 and some
3 odd patients per month, and, like I said earlier, a patient
4 base of over 25,000 patients, I have rather -- maybe 10, 5 to
5 10 percent of my patients that will have hypertriglyceridemia
6 to the effect of greater than 500 milligrams per deciliter.

7 But I will have 70 some odd percent of my patient
8 population which is characterized for the indication for
9 REDUCE-IT. So, they do affect very different patient
10 populations.

11 Q Now, do the defendants' labels in this case include both
12 of the indications that are on the Vascepa label?

13 A No, they do not. The defendants' label is consisted only
14 with what we have been categorizing as the MARINE indication,
15 which is the adjunct to diet to reduce triglyceride levels in
16 patients with severe hypertriglyceridemia.

17 Q And when you prescribe Vascepa for the MARINE indication,
18 do you prescribe it together with diet and exercise?

19 A Absolutely.

20 Q And do you generally prescribe Vascepa long-term?

21 A Generally, I do.

22 Q And why is that?

23 A Even though the testimony to follow will show it, and I
24 can tell you in my clinical practice we can see reductions in
25 triglycerides rather rapidly for the effects that I mentioned

04:45:26 1 previously, which are the reduction of cardiovascular problems
04:45:30 2 which is described above, the improvement in cholesterol
04:45:35 3 quality and particle size and density, and in the
04:45:38 4 anti-inflammatory properties.

04:45:41 5 If I'm able to get someone on this medication
04:45:43 6 long-term, I would like to use it long term. But the minority
04:45:47 7 of that is to reduce triglycerides in patients over
04:45:51 8 500 milligrams per deciliter.

04:45:53 9 Q So is the reason that you keep patients on Vascepa
04:45:55 10 long-term to keep their triglycerides below 500 as required by
04:45:59 11 the MARINE indication?

04:46:00 12 A Absolutely not.

04:46:01 13 Q So turning now to DDX 4.20, could you provide an example
04:46:07 14 of how you're able to use Vascepa with a typical patient.

04:46:11 15 A Yes. This is a slide I put together as an illustrative
04:46:16 16 example. So what it describes here as a first patient visit
04:46:20 17 after undergoing a lipid evaluation.

04:46:24 18 This individual has a triglycerides of
04:46:26 19 550 milligrams per deciliter. At the time of the visit, the
04:46:30 20 patient would undergo history, physical exam, other courses
04:46:35 21 of -- or other etiologies that would potentially be
04:46:39 22 contributing to hypertriglyceridemia would be discussed,
04:46:43 23 whether this patient is a smoker, if they're taking medication
04:46:46 24 that could potentially cause this, if they have diabetes, and
04:46:50 25 if they have hypothyroidism. These would be potentially

04:46:55 1 addressed at that time.

04:46:56 2 The patient would also be given a specific
04:46:59 3 nutritional plan and a specific exercise plan, either by
04:47:03 4 myself, or I would bring in an exercise physiologist and a
04:47:08 5 nutritionist who I have in my office.

04:47:10 6 And at the same time, that patient will be given
04:47:13 7 Vascepa or icosapent ethyl specifically because the
04:47:16 8 consequences of pancreatitis are so severe that I want to
04:47:21 9 address those risks absolutely as aggressively and as
04:47:26 10 thoroughly as I possibly can relatively immediately.

04:47:30 11 After the patient leaves the office, I will have he
04:47:34 12 or she return within a two- to four-month time period. I will
04:47:38 13 have a second set of labs drawn prior to the visit.

04:47:42 14 In this case the triglycerides have dropped to 300.
04:47:46 15 I'd like to point out the medication and the lifestyle
04:47:50 16 modification has successfully treated the severe
04:47:56 17 hypertriglyceridemic component. Even though this individual
04:47:58 18 is not yet at goal, where I want them, they are no longer in
04:48:02 19 the severe hypertriglyceridemic range, and at that point, a
04:48:06 20 decision is made.

04:48:08 21 More often than not, I will admit I do continue the
04:48:12 22 Vascepa. It has long-term risk reduction. It has those
04:48:15 23 tremendous benefits on advanced lipidology and advanced lipid
04:48:21 24 testing, and it has a discrete, definitive, anti-inflammatory
04:48:24 25 component.

04:48:25 1 But, there's a decent proportion of patients at that
04:48:27 2 time that I will discontinue the medication for various
04:48:30 3 reasons, and I will continue to instruct them -- in fact, it
04:48:34 4 is absolutely vital that they continue to make their diet and
04:48:39 5 exercise changes.

04:48:40 6 Most of the benefit we see in diet and exercise
04:48:43 7 changes do not occur in two to four months, it occurs over a
04:48:47 8 year. So we will continue to see that individual in the
04:48:49 9 clinic, we will continue to measure parameters, but there are
04:48:53 10 people who I will definitively stop this medication for and
04:48:58 11 continue aggressive lifestyle risk reduction.

04:49:01 12 Q Are there lifestyle interventions that can start
04:49:04 13 benefitting a patient before 12 weeks?

04:49:06 14 A Absolutely. So we can see discontinuation of smoking,
04:49:10 15 discontinuation of high-sugared beverages, and, again, the
04:49:15 16 reference we keep referring to is alcohol. But, again, where
04:49:18 17 I practice is Dr. Peppers, it's Big Gulps of 64 ounces of a
04:49:27 18 sugared soda, it is gummy bears.

04:49:30 19 So we can make those differences rather quickly by
04:49:34 20 convincing the individuals to change their habits.

04:49:36 21 Q Now, have you reviewed any data on how quickly Vascepa
04:49:40 22 can reduce triglycerides below 500?

04:49:43 23 A Yes, sir, I have.

04:49:43 24 Q So turning to DDX 4.21. There's snapshot on the screen
04:49:47 25 of DX 1694, page 214, and this is one of the exhibits on the

04:49:54 1 joint admitted list. Could you identify this document for the
04:49:57 2 record.

04:49:57 3 A Yes, I can. This is a clinical study report from the
04:50:02 4 MARINE study, and to take you through what we're looking at
04:50:06 5 here, it's the study of icosapent ethyl, and this is a summary
04:50:11 6 of the triglycerides in milligrams per deciliter. Circled is
04:50:16 7 week four, which is the fifth visit of the patient.

04:50:19 8 You look at the baseline initial evaluation, the
04:50:23 9 average -- I'm sorry, the median triglyceride level at
04:50:26 10 baseline was 679.5 milligrams per deciliter.

04:50:31 11 If you go down to the week four value, the median
04:50:35 12 has dropped to 471 milligrams per deciliter, and, again, that
04:50:42 13 third drop occurred by week four.

04:50:46 14 Q So according to Amarin's MARINE study, how long does it
04:50:51 15 take for Vascepa to lower triglycerides below 500?

04:50:55 16 A Four weeks, and I tell you this is also congruent with
04:50:59 17 what I see in my clinical practice.

04:51:01 18 Q So turning now to DDX 4.22, there's snapshot on the
04:51:05 19 screen DX 1701, page 68, which is also on the joint list of
04:51:10 20 admitted exhibits.

04:51:13 21 We've heard some testimony about this document, but
04:51:15 22 could you explain what you're showing on this slide for the
04:51:18 23 record?

04:51:19 24 A This is the FDA medical review for Vascepa from the
04:51:27 25 Center For Drug Evaluation and Research by the FDA.

04:51:27 1 This is a -- the paragraph below goes on to say that
04:51:31 2 the open extension MARINE, which was data up to 40 weeks, was
04:51:36 3 submitted as part of the 120-day update.

04:51:39 4 There is no figure described, but it describes that
04:51:41 5 the maximum triglyceride-lowering effect of 4 grams of Vascepa
04:51:46 6 occurred by week four, and the effects were maintained
04:51:49 7 throughout the study, and, again, this is what we see in the
04:51:54 8 clinical practice world.

04:51:57 9 Q So turning to DDX 4.23. There's another snapshot of
04:52:02 10 DX 1701, page 41.

04:52:04 11 Did you hear Dr. Budoff's testimony earlier about
04:52:08 12 the sentence "patients with very high triglycerides have a
04:52:12 13 strong genetic component to their decease," and it goes on?

04:52:15 14 A Yes, I did.

04:52:17 15 Q What does it mean for severe hypertriglyceridemia to have
04:52:20 16 a strong genetic component?

04:52:22 17 A Again, this is a -- it's a reiteration of what I
04:52:26 18 mentioned little bit earlier, and, that is, there needs to be
04:52:29 19 a definitive delineation here between a genetic abnormality
04:52:35 20 which results in a specific genetic issue and which an
04:52:39 21 individual has no other way around.

04:52:43 22 So, for example, if I have an individual who lacks
04:52:47 23 the gene for liposomal protein lipase, lipoprotein lipase, and
04:52:53 24 they have that genetic deficiency, that is a true genetic
04:52:53 25 abnormality.

04:52:58 1 But even as Dr. Budoff said there are people who
04:53:00 2 don't express think genetic abnormalities completely. There
04:53:05 3 are people who have genetic predispositions or genetic
04:53:06 4 proclivities to have things.

04:53:09 5 So patients with very high triglycerides levels
04:53:12 6 likely have a genetic component in some way to have
04:53:16 7 elevated -- elevated lipid issues whether it's triglycerides
04:53:20 8 or whatnot.

04:53:21 9 But it doesn't mean that their genetic differences
04:53:26 10 that we see within the patients make them unable to respond to
04:53:32 11 other interventions such as discontinuation of smoking,
04:53:35 12 engagement in proper exercise -- proper exercise regimens and
04:53:41 13 appropriate diet.

04:53:42 14 Q So are genetics the only component contributing to
04:53:47 15 patient severe hypertriglyceridemia?

04:53:49 16 A Absolutely not. Let me take this one step further and
04:53:53 17 definitively argue.

04:53:55 18 If I have a patient who's genetically predisposed to
04:54:01 19 be heavy, it may take us a little bit more dietary coaching or
04:54:06 20 a little bit more exercise prescription to get that person
04:54:10 21 where they need to be, but it doesn't mean it can't be done.
04:54:13 22 In fact, we do every single day.

04:54:19 23 Q So does everyone with a genetic predisposition for severe
04:54:33 24 hypertriglyceridemia require drug treatment?

04:54:35 25 A No, they do not.

04:54:36 1 Q So turning now to DDX 4.24, there's another snapshot of
04:54:42 2 DX 1701, page 41, which is still on the screen, and before I
04:54:47 3 get to the slide, what is your goal for triglycerides in terms
04:54:51 4 of the patients you treat?

04:54:54 5 A Ultimately I like to try to shoot for a triglyceride
04:54:57 6 level which is less than 150 milligrams per deciliter.

04:55:01 7 Q And are those normal triglycerides?

04:55:03 8 A That would be considered normal.

04:55:05 9 Q At what point does the FDA consider therapy with Vascepa
04:55:09 10 successful?

04:55:10 11 A They consider therapy successful in this population if
04:55:14 12 the triglycerides are lowered to less than 500 milligrams per
04:55:18 13 deciliter.

04:55:19 14 Q And does it take 12 weeks to achieve that success for
04:55:22 15 purposes of the indicated use?

04:55:24 16 A It does not.

04:55:25 17 Q Now, does Vascepa successfully reduce triglycerides in
04:55:29 18 all patients?

04:55:30 19 A It does not.

04:55:32 20 Q So turning to DDX 4.25, there's snapshot on the screen of
04:55:38 21 DX 1694, page 12, which we reviewed earlier.

04:55:44 22 According to the MARINE study report, are there
04:55:47 23 patients on Vascepa who do not experience triglyceride
04:55:49 24 reductions?

04:55:50 25 A Yes, that is correct. To look at this document, this is

an excerpt from the Amarin MARINE study, the Clinical Study Report.

What we're look at here which is highlighted is the percentage change from baseline to the 12-week evaluation. It's the endpoint in fasting triglycerides, and you can see at the bottom which highlighted, percent change from baseline, the median is 26.6 percent.

But if you look at what is described at Q1 and Q3, Q1 is the median in the first half of the group receiving this medication, the Q3 designation is the median of the second half of the group receiving this medication.

And you can see the median of that second half absolutely had a 0.0 percent change which means there are some people in this evaluation who actually had an increase in triglycerides, up to 25 percent of those people based on what we see here.

Q Does the MARINE Clinical Study Report also include data on LDL-C and apo B levels?

A Yes, it does.

Q So turning to DDX 4.26, there's a snapshot on the screen now DX 1694, page 268. According to the MARINE study report -- I'm sorry.

Are there patients taking Vascepa who's LDL-C increases according to the Clinical Study Report?

A Yes, this is the same type of data we just looked at on

the previous analysis. This is percent change in LDL from baseline to week 12.

And you can see, although there was median reduction of 4.5 percent, if you look at Q3, which is the median of the second half of the data group, there was an increase in LDL-C of 17.2, which means, again, that's the median, so there's a group of people in this evaluation who had an LDL increase above 17.2 percent.

Q And turning now to DDX 4.27, there's snapshot on the screen of DX 1694, page 239. Are there patients taking Vascepa whose apo B is not reduced?

A Yes, that is correct. Again, same document. It's laid out in the same way. This time we're looking apolipoprotein B.

Their percent change from baseline, the median was a reduction of 3.8 percent. But, again, if you look at that Q3 evaluation highlighted in yellow, you can see in that second half of the group that there was an actual 3.8 percent rise in apolipoprotein B which again indicates that are certain individuals, up to 25 percent, who had a rise which was even higher than 3.8 percent.

Q So turning to DDX 4.28, there are snapshots on the screen of DX 2248, DX 2256, and DX 2266. Could you identify these documents for the record.

A These are the package inserts or the labels for Vascepa

04:59:00 1 for Hikma's icosapent ethyl and Dr. Reddy's Laboratories'
04:59:06 2 icosapent ethyl.

04:59:06 3 MR. REIG-PLESSIS: And I believe DX 2248 and
04:59:10 4 2256 are already admitted, but we would move into evidence
04:59:14 5 DX 2266, which is the DRL label.

04:59:18 6 MS. KEANE: No objection, Your Honor.

04:59:20 7 THE COURT: 2248 is admitted.

04:59:25 8 MR. REIG-PLESSIS: And, I'm sorry, it was 2266.
04:59:27 9 I believe 2248 --

04:59:28 10 THE COURT: I'm sorry -- I looked at the first
04:59:30 11 one, 2248, 2256, 2266 are the three that are laid side by
04:59:35 12 side?

04:59:35 13 MR. REIG-PLESSIS: Correct, Your Honor. I
04:59:36 14 believe the first two --

04:59:38 15 THE COURT: I thought all of them were admitted
04:59:40 16 already. All the labels are in, aren't they?

04:59:42 17 THE CLERK: One was not, two was, 2266, Your
04:59:46 18 Honor.

04:59:46 19 THE COURT: The DRL label is not -- well, if it
04:59:49 20 hasn't been, it will be admitted.

04:59:49 21 (Defendants' Exhibit 2266 received in
04:59:52 evidence.)

04:59:52 22 MR. REIG-PLESSIS: Thank you, Your Honor.

04:59:53 23 I believe perhaps the PX version was previously
04:59:55 24 admitted, so we're moving into evidence just the 2266 DX
05:00:01 25 version.

05:00:02 1 THE COURT: Thank you.

05:00:02 2 MR. REIG-PLESSIS: Thank you.

05:00:03 3 BY MR. REIG-PLESSIS:

05:00:03 4 Q Dr. Sheinberg, are any differences between these three
05:00:07 5 labels, the Vascepa label, the Hikma label, and the DRL label,
05:00:13 6 material to any of your opinions relating to infringement of
05:00:18 7 the asserted claims?

05:00:18 8 A There is no difference.

05:00:19 9 THE COURT: I'm sorry, what was the answer?

05:00:19 10 THE WITNESS: I'm sorry, would you ask the
05:00:21 11 question again? I want to make sure I answer it properly.

05:00:21 12 MR. REIG-PLESSIS: Sure.

05:00:21 13 BY MR. REIG-PLESSIS:

05:00:23 14 Q Are there any material differences between the Vascepa
05:00:26 15 label, the Hikma label, and the DRL label, and when I mean
05:00:31 16 material, I mean differences that are material to your
05:00:34 17 noninfringement opinions.

05:00:34 18 A There's no difference, no material difference.

05:00:36 19 Q Are any differences between the Vascepa product and
05:00:39 20 defendants' generic products material to your opinions?

05:00:42 21 A No.

05:00:44 22 Q So let's move on to your noninfringement opinions. What
05:00:49 23 topics do you tend to address in your analysis?

05:00:52 24 A Well, now that we've finished the background, my
05:00:56 25 noninfringement analysis will effectively cover three

05:00:59 1 different topics, the 12 weeks duration topic, the lipid
05:01:02 2 effects topic, and the no concurrent lipid-altering therapy
05:01:06 3 topic.

05:01:08 4 Q What is the legal standard that you applied in analyzing
05:01:11 5 defendants' labels?

05:01:12 6 A The legal standard that I used is, quote,
05:01:15 7 "In order to induce infringement, the label
05:01:18 8 must encourage, recommend, or promote infringement.
05:01:22 9 Merely describing an infringing mode is not the same
05:01:26 10 as recommending, encouraging, or promoting an
05:01:29 11 infringing use, or suggesting that an infringing use
05:01:32 12 should be performed."

05:01:33 13 Q Now, just to be clear, Dr. Sheinberg, are you a lawyer?

05:01:36 14 A No, I am not.

05:01:37 15 Q Are you offering any legal opinions?

05:01:39 16 A No, sir, I am not.

05:01:40 17 Q Are you offering any opinions on FDA regulatory issues?

05:01:44 18 A No, sir, I am not.

05:01:46 19 Q Are you offering opinions from the perspective of a
05:01:49 20 physician?

05:01:49 21 A Yes, I am.

05:01:50 22 Q Now, as a physician, what parts of a drug label do you
05:01:54 23 generally expect to provide instructions on the duration of
05:01:59 24 treatment for a drug?

05:01:59 25 A Typically the areas that provide instruction are the

1 indication and usage and the dosage and administration
2 sections of the package insert.

3 Q So turning to DDX 4.31, there's snapshot on the screen
4 from DX 2256, pages 1 and 2. What are you showing on this
5 slide?

6 A This is the indication and usage section of the package
7 insert of defendants' label, and it goes on to describe
8 icosapent ethyl as indicated as an adjunct to diet to reduce
9 triglyceride levels in patients with severe
10 hypertriglyceridemia.

11 Q Now, to a physician, does the term severe
12 hypertriglyceridemia in the indication imply that indefinite
13 drug treatment is required?

14 A Absolutely not.

15 Q Is the indication for defendants' products limited to
16 patients with a genetic abnormality?

17 A It is not limited to any patient of any type.

18 Q So are the indicated uses for defendants' products
19 limited to chronic use?

20 A No, they are not.

21 Q And according to the indication, are defendants' products
22 a primary treatment for severe hypertriglyceridemia?

23 A They are not. They're adjunctive therapy which means
24 they need to be used in combination with diet.

25 Q So does the indications and usage section encourage

05:03:17 1 recommend or promote administering defendants' products for at
05:03:20 2 least 12 weeks?

05:03:21 3 A No, it does not.

05:03:22 4 Q Now, turning to DDX 4.32, were you in the courtroom when
05:03:27 5 Mr. Klein presented the testimony on this demonstrative from
05:03:31 6 Dr. Budoff during opening statements?

05:03:32 7 A Yes, I was.

05:03:33 8 Q And were you in the courtroom when Dr. Budoff confirmed
05:03:36 9 that testimony?

05:03:37 10 A Yes, I was.

05:03:38 11 Q And is your opinion consistent with Dr. Budoff's
05:03:41 12 testimony on this point?

05:03:42 13 A Yes, and to describe it, Dr. Budoff was asked and do you
05:03:46 14 agree it would still be consistent with the Vascepa labeling
05:03:49 15 for a doctor to prescribe Vascepa for fewer than 12 weeks, to
05:03:54 16 which Dr. Budoff replied yes.

05:03:58 17 Q Turning now to DDX 4.33. There's snapshot on the screen
05:04:02 18 of DX 2256, page 2. What are you showing on this slide?

05:04:07 19 A This is the dosage and administration section of the
05:04:10 20 package insert of defendants' drug, and under section 2.1 it
05:04:16 21 really goes on to describe what we've been talking about which
05:04:19 22 is obviously prior to initiation of icosapent ethyl assess
05:04:24 23 lipid levels which it's obvious, identify other causes which
05:04:28 24 we have talked about, and manage as appropriate, which I
05:04:32 25 testified earlier that would include treatment of those other

issues concomitantly with the use of lifestyle therapy and medication.

It goes on as second bullet to say patients should engage in appropriate nutritional intake and physical activity before receiving icosapent ethyl which should continue during treatment with icosapent ethyl.

Q Does the instruction to identify and manage other cases imply that medication should be delayed until those causes are addressed?

A Absolutely not. It's giving me sort of a direction that we need to fix underlying causes as appropriate, but it does not state that that should be done specifically prior.

And I would argue specifically against doing that because we understand the severe consequences in morbidity and mortality for pancreatitis, that we want to treat that as aggressively as we possibly can.

Q So focusing now on the second bullet under section 2.1, does the statement to engage in nutritional intake and physical activity before receiving icosapent ethyl mean that a patient should wait for diet and exercise to take effect before icosapent is administered?

A It's my interpretation of this that that is not the case. Again, ultimately, a goal for the prescribing physician is to make sure we keep our patients healthy and out of the hospital. In order to do so in this case, we have to keep

those people from developing pancreatitis.

So in terms of engaging in appropriate nutritional intake and physical activity, it does not specifically describe how long that should be, what it should be, and that's really up to the discretion of the prescribing physician.

I interpret this unequivocally to mean I have to make the appropriate nutritional and physical activity assessment and recommendations and then, in the same visit, prescribe the medication.

For example, if I have an individual who is a smoker, and I tell that individual after sitting with them and counseling them and showing them the risks, and I said to that individual, "I need you to stop smoking," and they say, "Okay, Doc, I understand, I'm going to stop smoking," well, that was a successful intervention right there. He immediately is engaged in appropriate smoking cessation.

The same thing holds true with alcohol consumption, or the example that I've been using this afternoon was the Dr. Pepper, and this is Texas where I grew up so Dr. Peppers are the thing out there, but it could be substituted for anything else.

But I can tell an individual, you know what, those Big Gulps of Dr. Pepper that you're drinking every day, it's not helping, in fact, that's causing your problem. The

05:07:18 1 patient can turn around say, "Okay, I understand, I'm done
05:07:21 2 with Dr. Peppers." Well, we just -- that patient just engaged
05:07:25 3 in appropriate nutritional effect.

05:07:30 4 Same thing goes physical with activity. It's
05:07:32 5 January 1st, the gyms are filled with people who, on
05:07:35 6 January 1st, are starting a physical activity program. They
05:07:41 7 may join a gym, they've engaged in physical activity.

05:07:44 8 So it's really at the discretion and interpretation
05:07:47 9 of the physician and how this sentence is actively utilized.

05:07:51 10 Q In your practice, do you delay administering drug therapy
05:07:55 11 when a patient presents with severe hypertriglyceridemia?

05:07:58 12 A I don't. I can't. In fact, I would argue along those
05:08:02 13 lines that if I have a patient that comes to my office with
05:08:06 14 severe hypertriglyceridemia, and I don't treat it aggressively
05:08:10 15 to the best of my ability, and that individual leaves my
05:08:13 16 office just to come back in four to six weeks for
05:08:17 17 reassessment, and they develop acute pancreatitis within those
05:08:22 18 four to six weeks, I feel that I have violated the standard of
05:08:26 19 care, that my colleagues would look at that and say why didn't
05:08:29 20 you treat this person when he was in your office.

05:08:31 21 Because the consequences are so severe, every
05:08:34 22 possible avenue of therapy needs to be addressed immediately
05:08:38 23 at that first visit.

05:08:39 24 Q So, in your opinion, is it an off-label use of Vascepa to
05:08:43 25 start Vascepa and diet and exercise at the same time?

05:08:47 1 A It is not.

05:08:50 2 Q So turning now to DDX 4.34, were you in the courtroom
05:08:54 3 when Mr. Klein presented this deposition testimony from
05:08:58 4 Dr. Budoff during opening statements?

05:08:59 5 A Yes, I was.

05:09:00 6 Q And were you in the courtroom when Dr. Budoff confirmed
05:09:04 7 this testimony?

05:09:05 8 A Yes, I was.

05:09:06 9 Q Is your opinion consistent with Dr. Budoff's testimony on
05:09:10 10 this point?

05:09:10 11 A Yes. And, actually, again, let me read it into the
05:09:14 12 record.

05:09:14 13 Dr. Budoff was asked,

05:09:16 14 "The dosage and administration section in the
05:09:18 15 Vascepa label leaves it entirely up to the
05:09:21 16 physician's discretion to determine the duration of
05:09:24 17 treatment. Do you agree?"

05:09:26 18 To which Dr. Budoff replied yes.

05:09:28 19 And, again, that is my understanding, and I do
05:09:31 20 agree that it is entirely up to the physician's discretion.

05:09:35 21 Q And just to turn back to DDX 4.33 for a moment, does the
05:09:40 22 reference to engaging in appropriate nutritional intake
05:09:46 23 require the patient to eat specific foods, or would it also
05:09:51 24 include restraining from eating certain foods?

05:09:54 25 A It really is a combination of both, and it has to be

05:09:58 1 addressed on a specific individual level, which takes into
05:10:01 2 consideration where that person is in terms of their
05:10:05 3 lifestyle, if there's any predisposing ethnic issues which
05:10:09 4 would predispose that individual to eat in certain different
05:10:12 5 food groups, if that person is a vegetarian, if they have
05:10:16 6 other dietary restrictions.

05:10:19 7 So it does not describe in any way, shape, or form
05:10:21 8 what that nutritional intake change should be here. It simply
05:10:26 9 tells me it needs to be what is described as, quote,
05:10:28 10 appropriate, unquote.

05:10:29 11 Q So in your example would ceasing to consume Big Gulps of
05:10:35 12 Dr. Pepper be engaging in appropriate nutritional intake or be
05:10:39 13 one component of that?

05:10:41 14 A Absolutely.

05:10:41 15 Q Now, have you compared defendants' labels to labels for
05:10:50 16 other drugs that actually specify duration of treatment?

05:10:52 17 A Yes, I have.

05:10:53 18 Q So turning first to DDX 4.35, there's a snapshot on the
05:11:01 19 screen of DX 1984, page 2. Could you identify this document.

05:11:05 20 A Yes, I can. This is the Lamisil label. Lamisil is an
05:11:10 21 antifungal tablet which we use for fingernail and toenail
05:11:15 22 infections, fungal infections.

05:11:17 23 MR. REIG-PLESSIS: And defendants would move in
05:11:19 24 the admission DX 1984.

05:11:21 25 MS. KEANE: No objection, your Honor.

05:11:22 1 THE COURT: DX 1984 is admitted.

05:11:22 2 (Defendants' Exhibit 1984 received in
05:11:22 evidence.)

05:11:22 3 BY MR. REIG-PLESSIS:

05:11:26 4 Q How does the dosage and administration section of the
05:11:26 5 Lamisil label compare to the same section in defendants'
05:11:31 6 labels?

05:11:31 7 A It's discretely different.

05:11:34 8 The Lamisil label goes on to specifically prescribe
05:11:37 9 a duration of therapy which is in complete contradistinction
05:11:41 10 to what is seen in the defendants' label, for example, for
05:11:43 11 fingernail onychomycosis which is a fingernail infection.

05:11:50 12 It specifically directs me to have the individual
05:11:53 13 use one tablet once daily for six weeks. For toenail
05:11:53 14 infections, it specifically instructs me to have an individual
05:12:03 15 take one tablet once daily for 12 weeks.

05:12:03 16 Q Have you ever prescribe Lamisil?

05:12:05 17 A Yes, I have.

05:12:06 18 Q So turning to DDX 4.36, there is a snapshot on the screen
05:12:11 19 of DX 1679 at page 5. Could you identify this document,
05:12:16 20 please.

05:12:17 21 A Yes, this is the dosage and administration section for
05:12:20 22 the package insert of what's called Lovenox which is
05:12:20 23 enoxaparin. It's an injectable low molecular heparin or an
05:12:20 24 injectable blood thinner.

05:12:29 25 In this case, they're describing the use of this

05:12:31 1 drug in the treatment of deep venous -- deep vein thrombosis
05:12:36 2 which is a clot with or without pulmonary embolism which is a
05:12:40 3 clot in the lungs.

05:12:41 4 The label goes on to specifically describe and
05:12:41 5 instruct the physician to initiate Warfarin which is Coumadin,
05:12:50 6 it's an oral blood thinner, when appropriate, and then
05:12:52 7 continue Lovenox for a minimum of five days and until a
05:12:57 8 therapeutic anticoagulant effect has been reach on the
05:13:03 9 Coumadin.

05:13:03 10 So, again, in complete contradistinction to
05:13:03 11 defendants' label, this label instructs a providing physician
05:13:08 12 to use this medication for a minimum duration of time that's
05:13:12 13 specifically spelled out.

05:13:13 14 MR. REIG-PLESSIS: Defendants' move the
05:13:15 15 admission DX 1679.

05:13:16 16 THE COURT: Isn't there already the Lovenox
05:13:20 17 label admitted earlier?

05:13:21 18 MR. REIG-PLESSIS: Your Honor --

05:13:22 19 THE COURT: Regardless, is there objection?

05:13:23 20 MS. KEANE: No objection.

05:13:24 21 THE COURT: All right. DX 1679 is admitted.

05:13:24 22 (Defendants' Exhibit 1679 received in
05:13:28 evidence.)

05:13:28 23 MR. REIG-PLESSIS: Thank you, your Honor.

05:13:28 24 And I believe some of the PX exhibits and DX
05:13:31 25 exhibits refer to the same documents because these

1 demonstratives were prepared before we knew what they would
2 admit.

3 THE COURT: All right. I remember Dr. Budoff
4 testifying as to the Lovenox label I think.

5 MR. REIG-PLESSIS: Thank you, your Honor.
6 BY MR. REIG-PLESSIS:

7 Q Turning now to DDX 4.37, there's snapshot on the screen
8 of DX 2256, page 7. What are you showing on this slide?

9 A This is the clinical study section of the defendants'
10 package insert or label in the clinical study section which is
11 described in 14.2 severe hypertriglyceridemia.

12 There's a reference to what we've described today as
13 the MARINE study, and I have highlighted here,

14 "Patients whose baseline triglyceride levels
15 were between 500 and 2,000 were enrolled in the study
16 which went on for 12 weeks in duration."

17 Q So does the clinical study section describe the use of
18 EPA for 12 weeks?

19 A It describes the use of EPA in this study for 12 weeks.

20 Q In your practice as a physician, do you look to the
21 clinical study section of a drug label for instructions on how
22 long to administer that drug?

23 A I do not. I look at the clinical studies section so I
24 can understand the rationale for using this.

25 It's simply -- what is described here is a simply a

discussion and a synopsis of what was seen in the reference trial.

Q To a physician, does the statement that the clinical trial lasted 12 weeks indicate that patients need to be treated for at least 12 weeks to reduce their triglycerides below 500?

A Absolutely not. It does not describe that or encourage that. It simply describes what was found in the study.

You can go further on to say, you know, if you look at the MARINE study, most of the individuals in the MARINE study were 53-year-old white males which doesn't correspond to the majority of my patient population anyway. So it's hard to extrapolate.

The only thing this description tells me is what was done in the MARINE trial.

Q So does the clinical study section encourage, recommend, or promote administering defendants' products for at least 12 weeks?

A No, sir, it does not.

Q So turning now to DDX 4.38, there are snapshots on the screen again of DX 2256, but now at pages 3 and 5. Are there any other references to a 12-week duration in defendants' drug labels?

A Yes, there are.

In section 6, which is the adverse reaction section,

05:16:01 1 they describe two randomized, double-blind, placebo-controlled
05:16:06 2 trials in patients with triglycerides between 200 and 2,000
05:16:10 3 who were treated for 12 weeks, and it describes the adverse
05:16:13 4 reactions that occur.

05:16:15 5 And in the second section, which is the clinical
05:16:19 6 pharmacology section under the pharmacodynamic subheading, it
05:16:24 7 describes a 12-week dose-ranging study in patients with severe
05:16:29 8 hypertriglyceridemia, and it describes it that it reduced the
05:16:31 9 triglycerides from baseline to placebo.

05:16:34 10 Q And, in your opinion, do these descriptions of a 12-week
05:16:38 11 duration encourage, recommend, or promote administering
05:16:41 12 defendants' products for at least 12 weeks?

05:16:43 13 A Again, absolutely not. This 12-week reference simply
05:16:47 14 describes in the first case two randomized studies that were
05:16:51 15 done looking at adverse reactions, and, in the second section,
05:16:56 16 it describes a dose-ranging study to show that there was
05:16:58 17 reduction in triglycerides relative to placebo.

05:17:00 18 But, again, these 12-week durations simply describe
05:17:05 19 what was seen in these limited studies, it does not in any way
05:17:09 20 indicate to me that that is how long I need to treat my
05:17:12 21 patients for.

05:17:13 22 Q So turning now to DDX 4.39, there's a snapshot on the
05:17:21 23 screen of DX 2256, page 9, and it's a snapshot from the
05:17:26 24 patient information section of defendants' labels.

05:17:29 25 Do you see the statement, "Do not change your dose

05:17:31 1 or stop taking icosapent ethyl without talking to your
05:17:34 2 doctor"?

05:17:34 3 A Yes, I do.

05:17:35 4 Q In your opinion, does that statement encourage,
05:17:37 5 recommend, or promote administering defendants' products for
05:17:41 6 at least 12 weeks?

05:17:42 7 A It does not. It simply instructs the patients to take
05:17:45 8 the medication that has been prescribed in the way it's been
05:17:48 9 given to you. Do not alter the medication without discussing
05:17:51 10 it with your own physician.

05:17:53 11 Q When a patient talks to his or her doctor, could the
05:17:57 12 doctor tell the patient to take the drug for less than
05:18:00 13 12 weeks?

05:18:01 14 A Absolutely. I receive at least a dozen phone calls a day
05:18:06 15 from patients, most of which are medication issues that need
05:18:10 16 to be resolved.

05:18:11 17 Often times after talking to the patient, I will
05:18:14 18 agree to stop that patient's medication well below the 12-week
05:18:19 19 limit or 12-week prescription.

05:18:22 20 Q And you may have testified to this before, but after
05:18:24 21 prescribing a drug like Vascepa to a patient, how long do you
05:18:28 22 usually wait before seeing that patient again?

05:18:31 23 A Anywhere between two and four months would be very
05:18:34 24 reasonable in my practice.

05:18:36 25 Q So do you sometimes see patients again before 12 weeks?

05:18:40 1 A Very frequently.

05:18:41 2 Q And have you told patients that it's okay to stop
05:18:42 3 Vascepa?

05:18:42 4 A I have.

05:18:43 5 Q And what are some of the reasons why a patient may want
05:18:45 6 to stop Vascepa?

05:18:46 7 A Well, if I have someone who has had a very successful
05:18:50 8 change in lifestyle, in other words, they're adhering to the
05:18:55 9 exercise prescription and nutritional recommendations that
05:18:57 10 we've made, we will stop the Vascepa because at this point,
05:19:00 11 they no longer need it.

05:19:02 12 There are also other reasons. Individuals can't
05:19:04 13 afford it. Some individuals have side effects. My experience
05:19:08 14 with this medication has been mostly GI or gastrointestinal
05:19:13 15 side effects. There are people who are eager to get off all
05:19:17 16 medications. So it is not infrequent that we stop medications
05:19:21 17 for these patients.

05:19:22 18 Q Is the size or number of pills a contributing factor in
05:19:27 19 patients' decisions?

05:19:28 20 A Without question. This is a difficult medicine to take
05:19:31 21 because it's a large number of pills, it's four pills. If
05:19:35 22 you've never seen these pills, patients joke and say they're
05:19:39 23 horse capsules, they're very large capsules, and there's a lot
05:19:42 24 of people that cannot swallow these capsules and simply
05:19:47 25 because of that reason want to stop their medication.

Q Now, on the screen is DDX 4.40 with another highlighted snapshot of the same page, DX 2256, page 9.

Does the patient information section suggest any other treatments for reducing triglycerides?

A Yes, it does. It says, "Your doctor may start you on a diet." It specifies what potential type of diet that would be, and it specifically says "stay on this diet while taking this medication."

Q So turning now to DDX 4.41, there's a snapshot on the screen of DX 2256, page 10.

If a physician decides to administer defendants' products long-term, is that necessarily for the indicated MARINE use of treating patients with triglycerides of at least 500?

A It's not. I testified earlier during this testimony that oftentimes we use this -- most often we use this medication for other reasons than the MARINE data, and in the patient information section it specifically tells the patients that we would potentially do that.

It describes a situation in which medicines are sometimes prescribed for purposes other than those listed in the patient information leaflet.

Now, as a prescribing physician I like to think we would talk to the patient and explain the reasons why, but this gives us full latitude in which in order to do so.

05:21:13 1 Q So taking defendants labels as a whole, do the labels
05:21:16 2 encourage, recommend, or promote administering defendants' for
05:21:16 3 at least 12 weeks?

05:21:20 4 A I'm sorry, can you repeat that one more time so I make
05:21:23 5 sure I answer the question properly?

05:21:23 6 Q Sure. Taking defendants' labels as a whole, do the
05:21:26 7 labels encourage, recommend, of promote administering
05:21:30 8 defendants' products for at least 12 weeks?

05:21:32 9 A No, they do not.

05:21:33 10 Q Do they express any preference for short-term versus
05:21:36 11 long-term use?

05:21:37 12 A The labels are completely silent in this regard, and
05:21:41 13 therefore and it is left up the discretion of the prescribing
05:21:45 14 physician.

05:21:46 15 Q What is the next set of claim limitations that you
05:21:48 16 analyzed?

05:21:48 17 THE COURT: Mr. Reig, how much longer do you
05:21:52 18 have for Dr. Sheinberg's direct examination?

05:21:56 19 MR. REIG-PLESSIS: Probably 15 more slides.
05:21:58 20 We've covered obviously the 12 weeks duration, but there are
05:22:02 21 two other categories of limitations.

05:22:05 22 THE COURT: I'm trying to assess whether it
05:22:07 23 makes sense to recess the testimony portion for today.

05:22:11 24 If you had about five minutes or so, I would let
05:22:14 25 you continue and then have plaintiffs start with the

05:22:18 1 cross-examination in the morning, but if you think you have
05:22:20 2 longer than five to ten minutes, I would probably pause and
05:22:23 3 recess for the day.

05:22:24 4 MR. REIG-PLESSIS: I would estimate that we have
05:22:26 5 probably little more than that, so a recess might make sense,
05:22:31 6 Your Honor.

05:22:31 7 THE COURT: We'll at least pause the testimony
05:22:33 8 portion for today. I want to have enough time to give you my
05:22:37 9 ruling on the Rule 52 motion earlier. So, at this time, let's
05:22:41 10 do that.

05:22:42 11 I'm going to ask Dr. Sheinberg to step down from
05:22:47 12 the witness stand.

05:22:47 13 THE WITNESS: Yes, your Honor.

05:22:47 14 THE COURT: And then we'll resume with your
05:22:49 15 testimony in the morning. I understand you have patients to
05:22:52 16 see, but, unfortunately, you have to return tomorrow.

05:22:55 17 THE WITNESS: That's okay.

05:22:56 18 MR. REIG-PLESSIS: Thank you, Your Honor.

05:22:57 19 THE COURT: All right. I will try to speak
05:23:18 20 slowly lest I get an instruction to slow down.

05:23:21 21 Here's my ruling on the Rule 52 motion.

05:23:25 22 Defendants asked for judgment under Rule 52(c)
05:23:29 23 as to plaintiff's induced infringement claim based on the
05:23:34 24 claim limitation presented in all of the asserted claims that
05:23:37 25 is requiring the administration of EPA for at least 12 weeks.

05:23:43 1 However, I will not enter judgment in
05:23:46 2 defendants' favor at this time because I find that plaintiffs
05:23:50 3 present sufficient evidence to satisfy the preponderance of
05:23:53 4 the evidence standard as to the 12-week limitation.

05:23:56 5 The question of whether defendants may be held
05:24:00 6 liable for inducing infringement turns on whether defendants
05:24:04 7 have, and I quote from the *Grunenthal* decision, this is at 919
05:24:10 8 F.3d 1333 at 1339, it's a Federal Circuit 2019 decision, and,
05:24:16 9 that is, defendants have -- the issue turns on whether
05:24:20 10 defendants have specific intent based on the contents of their
05:24:24 11 proposed labels to encourage physicians to use their proposed
05:24:29 12 ANDA products in a way that infringes the asserted claims.

05:24:32 13 In other words, I have to find -- I have to ask
05:24:36 14 whether the label, and I quote, encourages, recommends, or
05:24:39 15 promotes infringement. These are the terms that counsel have
05:24:42 16 used extensively throughout the examination and
05:24:45 17 cross-examination, and the PIN cite for that is the same, it's
05:24:48 18 at 1339.

05:24:49 19 And because the asserted claims are method
05:24:53 20 claims, I quote again, the pertinent question is whether the
05:24:56 21 proposed label instructs users to perform the patent method,
05:25:00 22 and the pin cite is the same at 1339.

05:25:02 23 Defendants' primary argue that their proposed
05:25:06 24 labels cannot be read to encourage, recommend, or promote
05:25:09 25 infringement of the 12-week limitation. However, Dr. Budoff

05:25:13 1 testified that reading the label as a whole, physicians would
05:25:16 2 be encourage to prescribe Vascepa or one of defendants' ANDA
05:25:22 3 drugs, the labels that are materially the same, for at least
05:25:25 4 12 weeks.

05:25:26 5 He testified that this is because a clinician
05:25:29 6 working in the field would know that STG, severe
05:25:39 7 hypertriglyceridemia, is largely a genetic problem requiring
05:25:43 8 long-term therapy.

05:25:45 9 Moreover, on cross-examination, Dr. Budoff
05:25:50 10 testified that STG is almost invariably a chronic condition.
05:25:56 11 He also testified to his own treatment practices describing
05:26:01 12 that he almost always prescribes Vascepa for more than
05:26:05 13 12 weeks and checks in with his patients about every three
05:26:09 14 months to monitor their lipid levels over the long term.

05:26:14 15 He also points to portions of the labeling
05:26:15 16 supporting his testimony that the proposed labels encourage
05:26:18 17 infringement of the 12-week limitation.

05:26:20 18 He specifically pointed to section 2.1 of the
05:26:23 19 labeling, and I'll refer to PX 1186, as I say, the labels are
05:26:28 20 the same, that is the December 2019 Amarin's label for
05:26:34 21 Vascepa.

05:26:35 22 He points to section 2.1 regarding what a doctor
05:26:40 23 needs do before initiating therapy with Vascepa. He testified
05:26:45 24 that this section of the labeling supports his testimony that
05:26:48 25 drug therapy using Vascepa is intended to be long-term. He

05:26:52 1 emphasized how the labeling tells doctors to first identify
05:26:56 2 other causes of STG and manage them as appropriate before
05:27:00 3 initiating therapy.

05:27:02 4 Therefore, a doctor would not begin Vascepa
05:27:06 5 therapy if the doctor can identify and remediate those other
05:27:09 6 causes such as diabetes.

05:27:11 7 Second, he testified that the labeling instructs
05:27:13 8 doctors to encourage patients to change their diet and get
05:27:17 9 more exercise before Initiating drug therapy. So he read the
05:27:22 10 labeling to require elimination of acute causes before
05:27:25 11 initiating Vascepa.

05:27:26 12 In other words, Dr. Budoff testified that the
05:27:29 13 only people left after removing the groups of people suffering
05:27:33 14 from acute causes of STG are people who have the genetic
05:27:38 15 disorder causing their elevated STG levels, and that is a
05:27:43 16 lifetime problem so doctors would initiate long-term therapy
05:27:47 17 for this chronic condition.

05:27:49 18 Now, defendants point to excerpts from
05:27:52 19 Dr. Budoff's testimony to argue that STG is not a chronic
05:27:56 20 condition, and on cross-examination Dr. Budoff acknowledged
05:28:00 21 that binge drinking, for example, can cause a spike in the TG
05:28:04 22 levels to over 500 milligrams per deciliter in patients who
05:28:10 23 are predisposed to high TG levels, and these patients can get
05:28:15 24 their TG levels back below 500 by cutting out alcohol if their
05:28:19 25 TG levels were sufficiently close to 500.

05:28:23 1 But he also explained that people who eat too
05:28:26 2 much or drink too much without an underlying medical issue
05:28:29 3 would not have STG, and, again, he explained that the label
05:28:33 4 instructs physicians to eliminate these acute cases first.

05:28:37 5 For those reasons I find that plaintiffs have at
05:28:39 6 least met their initial burden such that defendants are not
05:28:42 7 entitled to judgment of noninfringement on plaintiff's induced
05:28:47 8 infringement theory at this time, and the Rule 52(c) motion is
05:28:51 9 denied.

05:28:52 10 All right. With that we'll resume in the
05:28:54 11 morning at 8:30.

05:28:55 12 THE CLERK: Your Honor, may I ask clarification
05:28:58 13 please? I have not filed the minutes of yesterday yet because
05:29:01 14 of a question of a chart that may be produced by counsel with
05:29:06 15 regard to Mr. Klein's cross-examination. Should I go ahead
05:29:12 16 and submit my minutes as they are written?

05:29:15 17 THE COURT: Why don't you submit the minutes,
05:29:18 18 and the chart that will be created, counsel can file that on
05:29:23 19 the docket.

05:29:28 20 There is -- I probably should resolve the
05:29:34 21 evidentiary issue raised at the end of yesterday about the 25
05:29:38 22 additional exhibits. I don't know if counsel -- Mr. Rounds,
05:29:42 23 if you have identified which expert or which documents will be
05:29:49 24 used with which expert because I don't know if they'll up
05:29:53 25 tomorrow.

05:29:53 1 MR. ROUNDS: Yes, we did that last night, your
05:29:56 2 Honor, and, no, they're not up tomorrow.

05:29:57 3 THE COURT: Will they be up Friday?

05:29:59 4 MR. ROUNDS: No, not as far as I know.

05:30:01 5 THE COURT: Well, I've looked at the exhibits,
05:30:03 6 and my preliminary reaction is I don't think that it supports
05:30:08 7 the -- while I realize that there are -- well, let me describe
05:30:13 8 what the exhibits are. Give me one moment.

05:30:33 9 So there were 25 exhibits and they're various
05:30:38 10 categories and they are exhibits that were produced by Amarin.
05:30:41 11 I think they're about 136 pages, although there were a few
05:30:47 12 blank pages. They include the drafting labeling for the EPA
05:30:55 13 capsules, there's an article by an Amarin employee about the
05:31:00 14 MARINE and the ANCHOR studies, 1099 tax forms for a company,
05:31:08 15 some e-mail exchanges, the CV of Edward A. Fisher, I assume
05:31:15 16 he's one the witnesses.

05:31:16 17 My point is, while I agree with Amarin that
05:31:22 18 deadlines are there for a reason, they're -- they're there to
05:31:26 19 ensure fair play and that there's no ambushing of any of the
05:31:30 20 attorneys or counsel at trial -- or the witnesses at trial, so
05:31:35 21 I expect -- and I'm very rule-oriented person. I expect
05:31:39 22 counsel to follow the rules.

05:31:41 23 But I do understand that given the voluminous
05:31:44 24 nature of the exhibits in this case, and the complexities of
05:31:47 25 the testimony of the witnesses, that -- such that I will

1 accept the explanation for the delay in identifying these
2 additional exhibits.

3 And because of the volume, because of the fact
4 that they were documents produced by Amarin, I don't -- I'm
5 not persuaded by the argument that there's prejudice to Amarin
6 if I don't exclude the additional exhibits, and that's the
7 main reason why I'm going to permit the exhibits to be
8 offered. Whether or not individually they will be admitted at
9 trial is a different issue, but I'm not going to exclude them
10 for their late disclosure.

11 Therefore the motion that was filed orally
12 yesterday to exclude the additional 25 exhibits is denied.

13 I expect going forward that counsel will comply
14 with the rules. I know that you're updating your exhibit
15 lists constantly, and I understand that there's fluctuations
16 during the trial. Peggie has probably already reminded you
17 that when you do that, you need to give me the updated
18 exhibits and the updated exhibit list.

19 Okay. With that we'll resume in the morning.

20 (The evening recess was taken.)

21 -o0o-

22
23 I certify that the foregoing is a correct
24 transcript from the record of proceedings in the
above-entitled matter.

25 /s/ Kathryn M. French

1/25/2020

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Kathyrn M. French, CCR #392, RPR

Date

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